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The Role Of The Septum In Water Intake And Satiety Mechanisms

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THE ROLE OF THE SEPTUM IN WATER INTAKE AND SATIETY MECHANISMS

by

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ABSTRACT

The purpose of the research presented in this thesis was to investigate the nature of the hyperdipsia resulting from lesions of the septal region of the rat brain.

In the first part of the study, the phenomenon of septal hyperdipsia was examined, and it was found that septal rats are hyperdipsic, as opposed to polydipsic, and that the normal pattern of drinking and feeding is not disrupted by damage to the septum. Rather, the septal rat drinks for a longer period than controls once water intake has been initiated. Increased water intake did not seem to be related to increased thirst, since rats with septal lesions would not work to obtain excess water when several responses had to be made to obtain a water reward. These results suggested that septal damage results in an inability to utilize short-term satiety cues.

In the second part of the study, the hypothesis that the septum is involved in an inhibitory or satiety system for the control of water intake was examined. In addition, an attempt was made to determine the locus of the septal lesion which produces hyperdipsia. The results indicated that the septum exerts an inhibitory influence upon the hypothalamic integrative-control system for water intake, and that it is concerned with the termination of drinking.

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CHAPTER 1

Water, and its exchange with the environment, is of critical importance for living organisms. Complex regulatory mechanisms have evolved whereby the water content of the body is regulated within fine limits. A good deal of research in recent years has emphasized the importance of the hypothalamus in the control of drinking behaviour since electrical and chemical stimulation of the lateral hypothalamus result in drinking while lesions of the same area produce adipsia.

Other regions of the brain, especially the limbic system, are involved in the control of water intake, water balance and other homeostatic functions. Since lesions of the septum increase water intake substantially there has been increasing interest in its role in water balance. The present study, concerned with the mechanisms of septal hyperdipsia, provides evidence that the increased water intake from septal lesions is probably not due to increased thirst. The results suggest that the lesions produce a

deficit in the termination of water intake and that the septum is part of an inhibitory or satiety system.

The introduction consists of a brief summary of the known aspects of hypothalamic control of water intake, followed by a discussion of the influences exerted upon the hypothalamus by other diencephalic and telencephalic structures, with special attention paid to the role of the septal region.

HYPOTHALAMIC REGULATION OF WATER INTAKE

As indicated in a number of reviews (Wolf, 1958; Andersson, 1966; Stevenson, 1967), water intake is controlled by several factors. The main signals of a water deficit are increased osmotic pressure of body fluids and hypovolemia (isosmotic depletion of the vascular volume, Stricker, 1969). In addition, temperature and prandial (dry-mouth) cues may initiate drinking. These signals are believed to influence an integrative-control system in the brain.

That the lateral hypothalamus is an important component of the integrative-control system for water intake is suggested by several experimental studies. Electrical stimulation of the lateral hypothalamus elicits drinking (Greer, 1955), even in the absence of systemic dehydration (Andersson, Larsson and Persson, 1960). Prolonged electrical stimulation leads to hyperdipsia and polyuria (Mogenson and Stevenson, 1966, 1967). The

application of cholinergic agents to the lateral hypothalamus also induces drinking behaviour (Grossman, 1960, 1962). Lesions of the same area result in adipsia without aphagia (Montemurro and Stevenson, 1957), demonstrating that the lateral hypothalamus is essential for drinking behaviour. The lateral hypothalamus is thought to receive inputs from receptors that signal water deficit and to initiate and maintain drinking.

The long-term regulation of water intake and water balance is probably controlled by osmotic regulation (Stevenson, 1969). However, the literature on the temporal course of drinking indicates that many species are capable of replacing a water deficit in a very short time, before any appreciable absorption of water from the stomach occurs. In the dog for example, the entire water deficit is replenished rapidly and in one uninterrupted period of drinking (Adolph, 1943). Rats drink more slowly, and long pauses begin as soon as a significant percentage of the deficit is restored (Adolph, 1943). Nevertheless, the fact that pausing occurs suggests the existence of a temporary satiety effect.

What is the nature of the information which results in the termination of drinking? Bellows (1939) reported that dogs with esophageal fistulas, in which ingested fluid does not reach the stomach, drank larger volumes of water than was actually required to restore a

fluid deficit. However, these animals did not drink constantly but rather, drank for a while, stopped, and then drank again. Bellows proposed that the brief pauses might follow the metering of the ingested fluid by some oral receptor. Zotterman (1949, 1956) has shown that several species have water receptors on the tongue which respond selectively to water, and it is possible that they play a role in oral-pharyngeal metering of water intake. Stomach distension also appears to play some role in the metering of water intake and in the inhibition of drinking (Towbin, 1949, 1955, 1964; Miller, Samlinger and Woodrow, 1957).

It has been suggested that information concerning the amount of water taken in is relayed to the central nervous system and activates mechanisms which produce a temporary termination of drinking (Oatley, 1967). What is the locus of the neural inhibitory system? Presumably, ablation of a thirst satiety center or area should lead to excessive drinking analagous to the hyperphagia which results from destruction of the ventromedial nuclei of the hypothalamus. Although there was an early suggestion of primary hyperdipsia in diabetes insipidus (Bailey and Bremer, 1921; Snell, 1929), the evidence was meager and inconclusive, and the concept of a central satiety system

for water intake has not been emphasized (Stellar, 1954; Brobeck, 1960). Recently, Stricker (1969) has shown that with volumetrically induced thirst (hypovolemia), drinking ceases before the plasma deficit is restored. Furthermore, cellular hydration is sufficient to inhibit hypovolemic thirst (Stricker, 1969). Stricker has suggested the possibility of an inhibitory or satiety system for water intake based on osmotic dilution. He proposed further, that this system may involve the anterior hypothalamus and/or structures of the limbic system, since lesions placed in these areas may result in primary hyperdipsia (Smith and McCann, 1962; Lubar, Boyce and Schaefer, 1968). More empirical evidence concerning the functions of these areas is required however, before Stricker's suggestion can be evaluated.

EXTRA-HYPOTHALAMIC INFLUENCES ON WATER INTAKE

There were several early indications that extra-hypothalamic structures are involved in the control of water intake and water balance. The importance of fore-brain influences in water and energy balance was demonstrated by Bard and Rioch (1937) who showed that animals lacking much of the telencephalon would reflexively chew and swallow food and water placed directly into the mouth, but would not actively seek out food or water. Apparently, the guiding and motivational aspects of consummatory

behaviour, are mediated by neural tissue rostral to the thalamus.

More recent evidence, from studies involving electrical and chemical stimulation and surgical intervention techniques, has demonstrated that structures other than the hypothalamus, particularly those of the limbic system are also involved in the control of water intake. Robinson and Mishkin (1962) and Robinson (1964) explored portions of the limbic system and diencephalon and elicited drinking by electrical stimulation of the anterior cingulate gyrus and midline thalamus. Drinking could also be elicited from other structures close to, or anatomically associated with, the limbic system. Fisher and Coury (1962) and Coury (1967) have attempted to trace the system rostral to the hypothalamus in the rat employing cholinergic stimulation. The results of their studies indicate that those sites from which drinking can be elicited lie primarily within the limbic system. Thus, the application of carbachol to the hippocampus, the septum, the fornix, the mammillary bodies, the mammillo-thalamic tract, the anterior thalamus and the cingulate gyrus was found to result in increased water intake (Fisher and Coury, 1962, 1964; Coury, 1967). Grossman (1964) found that cholinergic stimulation of the amygdala failed to affect water intake in rats

satiated for water, but nearly doubled water intake when the animals were food and water deprived, suggesting that this structure is involved in some sort of modulating system. The drinking system of the limbic system can apparently be selectively activated by cholinergic stimulation. Drinking cannot be elicited by the application of drugs of other classes to limbic areas. The local application of an anti-cholinergic agent, on the other hand, may inhibit drinking, especially that in response to cholinergic stimulation, but also, to a lesser degree, that induced by water deprivation (Grossman, 1964; Levitt and Fisher, 1967).

Experiments employing electrolytic lesions have also demonstrated the importance of some limbic structures in the regulation of water intake. Increased water intake has been observed following destruction of the hippocampus (Kimble and Coover, 1966), the septum (Harvey and Hunt, 1965), the fornix (Pizzi and Lorens, 1967), the cingulate cortex (Lubar and Wolfe, 1964) and the posterior amygdala (Grossman, 1964). While the evidence concerning the severity and permanence of the hyperdipsia following some of these lesions is equivocal, it seems clear that lesions of the septum at least, result in a 30 to 40 percent increase in water intake (Harvey and Hunt, 1965; Carey, 1967, 1969; Lubar, Boyce and Schaefer, 1968; Lubar, Schaefer and Wells,

1969). Harvey and Hunt (1965) reported that the increase in water intake lasted up to seven months after surgery, indicating that lesions of the septum may lead to permanent hyperdipsia.

Gilbert (1957) reported that hypodipsia, and occasionally adipsia, results from lesions of the subcommissural organ, implicating this structure in the regulation of water intake. More recent evidence however, indicates that destruction of the subcommissural organ results in only a temporary disruption of water balance (Upton, Dunihue and Chambers, 1961), and more research is required before any definite conclusions can be drawn about the functions of the subcommissural organ and its possible role in water intake.

Although the hypothalamus is a crucial structure for the maintainence of drinking behaviour, it appears that the system controlling water intake extends rostrally into the limbic system and, perhaps, includes cortical areas (Andersson and Larsson, 1956; Buresova, Rudiger, Bures and Fifkova, 1962). The precise role of these extra-hypothalamic regions has not yet been determined. Fisher and Coury (1964) have speculated that, since the limbic system and cerebral cortices are the recipients of many inputs from both internal and external sources, it is the function of this complicated neural system to integrate this informa-

tion and to provide the energizing and guiding aspects to consummatory behaviour. Unfortunately, there is little empirical evidence to permit a critical evaluation of this suggestion.

This thesis is concerned with one component of the system described above, the septum, and with its role in the regulation of water intake. The following sections provide an anatomical description of the septal area of the rat brain and a summary of the experimental studies of this limbic structure.

THE SEPTUM

The septal area lies beneath the anterior half of the corpus callosum and is bounded anteriorly by the precommissural hippocampus, posteriorly by the hippocampal or fornical commissure, and laterally by the lateral ventricles. Postero-ventrally, the septum is limited by the anterior commissure, while anteriorly it merges with the olfactory tubercle and the preoptic area. Although some confusion exists as to those nuclei which comprise the septum, the anatomical descriptions provided by Andy and Stefan (1964), based on phylogenetic studies of this structure are the most complete and comprehensive. These authors recognize four major nuclear groups--dorsal, ventral, medial and caudal--each consisting of one or more nuclei. The

dorsal group, extending throughout the entire length of the septum includes the nucleus septalis dorsalis which is subdivided into anterior, external, intermediate and internal areas. The ventral group, which also runs from anterior to posterior septum is made up of the nucleus septalis lateralis, subdivided into internal and external parts. The medial group consists of the nucleus septalis medialis (pars anterior and pars posterior), and the nucleus of the diagonal band of Broca (pars dorsalis and pars ventralis). These nuclei are found primarily in the anterior portion of the septum. Four nuclei comprise the caudal group--the nucleus septalis fimbrialis, the nucleus septalis triangularis, the bed nucleus of the anterior commissure and the bed nucleus of the stria terminalis.

The septum is anatomically situated so as to occupy a strategic position between the older structures of the diencephalon and the telencephalon. Its afferent and efferent connections, which are summarized by Raisman (1966), reflect its central location. All nuclei of the septum, with the exception of the bed nucleus of the stria terminalis, receive fibers from the hippocampus through the fornix. Afferent fibers from the hypothalamus and midbrain ascend to the medial septal region via the medial forebrain bundle. The amygdala also maintains afferent connections

to the septal region through the stria terminalis. The major telencephalic efferents of the septum are directed towards the hippocampus, thus establishing two-way connections between these structures. The septum is also a major source of efferent fibers coursing in the medial forebrain bundle and terminating primarily within the hypothalamus and in the ventral tegmentum. All parts of the septum, but particularly the nucleus septalis fimbrialis, contribute fibers to the stria medullaris which continues posteriorly to the habenular complex.

The septum is thus in a position which enables it to influence the functions of both higher and lower brain areas. In this respect, the connections between the hippocampus and septum and between the septum and the hypothalamus deserve special attention. The septum appears, in this case, to function as a relay area for information proceeding from hypothalamus to hippocampus and vice versa. However, since direct connections exist between the hippocampus and the hypothalamus via the fornix, the septum probably performs some sort of integration of the information it receives before passing it on. Although the nature of this integration is unclear, the commonality of dysfunction following lesions of the septum or hippocampus (McCleary, 1966; Wishart and Mogenson, 1970) and septum or

ventromedial hypothalamus (Singh and Meyer, 1968), may shed some light on this matter.

SEPTAL INFLUENCES ON WATER REGULATION

The first indication that the septum plays some role in the control of water intake came from the results of chemical stimulation experiments (Fisher and Coury, 1962; Grossman, 1964). Cholinergic drugs applied locally to the septal region were found to initiate drinking which lasted for 20 to 30 minutes. The average intake of six animals tested in the Fisher and Coury (1962) experiment was 14 milliliters, while the maximum intake was 31 milliliters. Grossman (1964) reported that the drinking behaviour of 24 hour water deprived animals could be inhibited by placing atropine (an anti-cholinergic drug) into the septum. With the exception of the dorso-medial hippocampus, the septal region was found to be the most potent of the limbic structures for producing these effects, and the response to cholinergic stimulation of the septum appears to be more pronounced than that in response to chemical stimulation of the lateral hypothalamus (Grossman, 1960, 1964). Fisher and Coury (1962) suggested that a system which facilitates water intake, courses through the hippocampus and septum.

More recent evidence indicates that the effects

of cholinergic stimulation of the limbic drinking system are not identical to normal drinking induced by water deprivation. Levitt and Fisher (1967) found that atropine, applied to the septum, blocked carbachol-induced drinking but did not inhibit, to the same degree, drinking from water deprivation. Some differences between carbachol-induced and deprivation-induced drinking have also been reported by Gandelman, Panksepp and Trowill (1968). Carbachol-induced drinkers were found to select a sucrose solution in a preference test while water-deprived animals preferred water. These observations suggest that the chemical agents applied to the brain to increase water intake may also influence systems concerned with other behaviours.

Hunt and Harvey (1964) were the first to report increased post-operative water intake following lesions of the septum. In subsequent experiments (Harvey, Lints, Jacobson and Hunt, 1965; Harvey and Hunt, 1965), they found that septal animals drank, on the average, 30 to 40 percent more water than operated controls when water and food were available ad libitum.

Evidence regarding the size and locus of the lesion within the septum which produces hyperdipsia is conflicting. Harvey and Hunt (1965) obtained results

indicating that lesions of the septum rostral to the anterior commissure produced excessive water intake. This observation was supported by the findings of Donovick and Burright, 1968). However, Lubar et al. (1968, 1969) reported that it is damage to the posterior one-third of the septum which disrupts water balance. Pizzi and Lorens (1967) destroyed the fornix and posterior septum and found increased water intake, thus supporting the findings of Lubar and his associates. Carey (1969) found that while both anterior and posterior lesions of the septum resulted in increased water intake, only animals with anterior lesions were motivated to drink to excess. In a recent study (Besch and Van Dyne, 1969), ventral septal lesions which led to cell damage or degeneration in the paraventricular nuclei appeared to be positively correlated with increased water intake. The interpretation of these results is complicated by the fact that, in all cases, rather large lesions were made, destroying simultaneously many nuclear regions. More experimental work is required to account for these differences and to define the anatomical locus of septal hyperdipsia.

Harvey and Hunt (1965) postulated that septal hyperdipsia is due to the disruption of the system which controls the release of antidiuretic hormone (ADH). This,

of course, would lead to decreased secretion of ADH and decreased reabsorption of water by the kidney. Thus, the hyperdipsia observed was postulated to be secondary to the increased loss of water from the body as urine. Some support for this hypothesis was obtained by Usher, Kasper and Birmingham (1967) who observed that animals with septal lesions excrete excessive amounts of dilute urine containing more sodium ion than normal. Lubar, Schaefer and Wells (1969) also observed that septal animals excrete large volumes of dilute urine, and showed that injections of pitressin tannate (ADH) restored both urine volume and osmolality to pre-operative levels.

The results of subsequent investigations have indicated that the increased water intake from septal lesions is not secondary to excessive urine output. In the Lubar et al. (1969) study, cited above, the magnitude of the hyperdipsia was merely reduced rather than entirely eliminated during ADH replacement therapy which successfully restored urine volume and osmolality to normal levels. This was a clue suggesting that increased water intake is a primary effect of septal damage. Lubar et al. (1968) tested rats with septal lesions using the Hickey-Hare test which involves the administration of hypertonic sodium chloride. If the rat is not permitted to drink, the normal

response is increased secretion of ADH by the neurohypophysis. This results in increased reabsorption of water by the kidney so that a highly concentrated urine is excreted. Animals in which the ADH system has been disturbed are incapable of concentrating their urine, and continue to excrete large volumes of urine. Lubar et al. (1968) showed that normal rats and rats with septal lesions did not differ in their responses to a hypertonic saline load. Both the average volume and the osmolality of the urine excreted by the animals in the two groups were similar. Lubar and his associates concluded that the hyperdipsia following septal lesions is primary.

If, as suggested in the preceding paragraph, the hyperdipsia is not secondary to excessive urine output, what is the cause of the increased water intake following septal lesions? To answer this question, some investigators have examined the septal rat's response to the various physiological stimuli known to induce drinking. The evidence so far indicates that septal animals do not overrespond to osmotic, thermal or prandial cues. Lubar et al. (1968) and Blass and Hanson (1970) have shown that septal animals drink the same amount of water and excrete the same amount of urine as normal controls when osmotically stressed by injections of hypertonic saline. Septal animals also appear

to be normal in their response to thermal cues. The core temperatures of septal rats were found to be similar to those of controls even after several hours of cold stress (Heller, Harvey, Hunt and Roth, 1960), indicating that septal lesions do not disrupt the thermoregulation system. Furthermore, rats with septal lesions did not drink more water than controls in the heat (Tegart, unpublished observations). Finally, Blass and Hanson (1970) have shown that septal animals do not drink excessively or more frequently than controls in response to prandial cues.

It should be pointed out that if the septal animal is deficient in its response to one or more of the primary cues which initiate drinking, hypodipsia rather than hyperdipsia should occur. Hyperdipsia can only follow the removal of some dampening or inhibitory influence. Thus, the increased water intake of rats with septal lesions is likely due to a release from inhibition which the septum exerts on the integrative-control system for water intake. Blass and Hanson (1970) reported that rats with septal lesions overresponded and drank larger volumes of water than normal controls in response to hypovolemia. They suggested that "the etiology of septal hyperdipsia resides in a removal of the inhibition normally exerted on hypovolemic drinking" (p. 93). The nature of this inhibitory

mechanism, however has not been elucidated.

The role of the septum in the control of water intake has also been studies using electrical stimulation. Kasper (1965), using direct current stimulation of the septum, was unable to show any effect on ad libitum water intake. It is possible, however, that this type of stimulation produced small lesions around the electrode tip, accounting for the negative results. Mabry and Peeler (1969) found a decrease in water intake during a one-half hour testing session following water deprivation when alternating current was delivered to the septum. Reduced consumption of sucrose and slower rates of lapping were observed by Asdourian (1962) when septal stimulation was contingent upon lapping. These findings are consistent with the suggestion that the septum has an inhibitory effect on water intake, but further studies of the septum using the electrical stimulation technique seem to be warranted.

Steiner (1962) attempted to show that the neural activity of the septum, and other subcortical areas, is influenced by appetitive drives. He recorded the electrical activity of the septum and showed that the amplitude of the potentials decreased as the degree of water deprivation increased. Steiner argued that this change reflected the influence of a drive or motivational system on the septum.

This effect does not appear to be specific to the septal area however, since similar results were obtained with recordings from many other subcortical areas.

In summary, the septal area has been shown to be directly involved in the control of water intake. The local application of cholinergic agents to the septum increases water intake, whereas anti-cholinergic stimulation of the same area depresses drinking. Lesions of the septum disrupt water balance by causing excessive water intake while alternating current stimulation may reduce water consumption. As yet, little is known about the role of the septum in the maintainence of water balance. It does not seem to be involved in monitoring the primary signals of thirst for, as pointed out above, if this was the case, then hypodipsia would follow the destruction of septal tissue. It is more likely that the septum exerts its effects on water intake by maintaining an inhibitory influence over the lateral hypothalamic drinking system. In most previous investigations of septal hyperdipsia, this hypothesis has not been given serious consideration.

SEPTAL INFLUENCES ON FOOD INTAKE AND ENERGY BALANCE

Since water intake is related to food intake, it is possible that septal hyperdipsia occurs as a result of increased food consumption. Some experimenters have

ported the occurrence of increased food intake following
ptal lesions (Simmons and Thomas, 1961; Wolfe, 1965;
ngh and Meyer, 1968). Reynolds (1962) found that lesions
the dorsal-posterior septum increased food intake whereas
sions of the ventral-posterior septum resulted in no
fect or led to reduced food intake. However, other
perimenters have been unable to find any differences in
od consumption between animals with lesions of the septum
d normal controls (Zucker, 1965; Lorens and Kondo, 1969;
bar et al., 1969). Furthermore, Harvey and Hunt (1965)
owed that septal hyperdipsia does not depend on altera-
ons in food intake since food restriction did not elimi-
te the increased water intake.

That the septum does exert an influence on food
take has been demonstrated by chemical stimulation experi-
nts. Application of norephinephrine to the septum has
en found to elicit eating in rats satiated for food
ooth, 1967; Coury, 1967). Electrical stimulation, on
the other hand, depresses feeding in monkeys (Rubenstein
and Delgado, 1963) and cats (Fonberg and Delgado, 1961),
although 'rebound' feeding has been observed following the
termination of stimulation of the septal region in rats
(MacLean, 1959; Altman, 1970; Wishart and Bland, 1970).

FECTS OF SEPTAL DAMAGE ON THE MOTIVATIONAL ASPECTS OF
NSUMMATORY BEHAVIOUR

Harvey and Hunt (1965) suggested that the increased
ter intake following septal lesions is due to increased
irst. This suggestion was based on the results of experi-
nts in which rats with lesions of the septum, as well as
erated controls, were required to perform an operant res-
nse to obtain water. On fixed interval (FI) and continuous
inforcement (CRF) schedules, rats with septal lesions
de more lever presses for water than did controls during
e hour daily tests. When required to wait a specified
me before responding (differential rates of low rein-
rcement, DRL), the septals responded like the controls,
in some cases, tended to make fewer responses and thus
came more efficient at obtaining rewards. Harvey and
nt reasoned that the behaviour of the septal animals was
ch as to maximize the number of rewards received, and
at this increased motivation for water was due to the
increased thirst of these animals. In support of this
hypothesis, Harvey and Hunt observed that decreasing the
difference in thirst between the septal and control animals
(either by placing the controls on a longer water depri-
vation schedule or by differential pre-watering of the
septal animals), reduced the magnitude of the difference

between the two groups in the operant situation.

Ellen and Powell (1962) did not observe increased rates of bar pressing by septal animals on FR schedules of reinforcement. Furthermore, higher terminal rates of pressing on FI schedules led these investigators to postulate that rats with septal lesions are hypersensitive to water rewards, and that this hypersensitivity, rather than increased motivation for water, was responsible for the effects they observed. Other experimenters have also concluded that the effect of septal damage, as measured by the operant technique, is primarily on reinforcement mechanisms. This hypothesis was elaborated by Zucker (1965) who suggested that the normal function of the septal area might be to dampen the increase in response strength which usually follows a reinforcement. Therefore, damage to the septal area should be expected to increase the rewarding properties of reinforcing stimuli. In support of this hypothesis, Raphaelson, Isaacson and Douglas (1966) and Clody and Carlton (1969) found increased running speeds and increased resistance to extinction by rats with septal lesions in simple approach tasks. Pubols (1966) and Buckland and Schwartzbaum (1970) have found increased rates of lever pressing for sucrose rewards following septal lesions.

A third hypothesis has been offered to explain these results. In tests of passive avoidance, animals with septal lesions are found to return more readily and more often to a place where shock has been given (McCleary, 1961). Rats with limbic damage seem unable to sit on a small wooden island in the middle of an electrified grid despite repeated shocks for leaving it (Teitelbaum and Milner, 1963). This type of deficit has been termed response perseveration (Ellen and Wilson, 1963), or an inability to inhibit prepotent responses (McCleary, 1961), two similar concepts. Thus, increased lever pressing rates, faster running speeds and prolonged extinction have all been attributed to the elimination of the somato-motor inhibitory influences of the septal area (Burkett and Bunnell, 1966). However, it has been shown that the effects of septal lesions on water intake and response inhibition are independent and separable (Carey, 1967). Carey (1967) showed that rats with lesions of the anterior septum which increased their ad libitum water intake, respond normally in operant tasks employing DRL. In contrast, posterior septal damage had no effect on water consumption but markedly increased the number of responses emitted in the operant test. In a second study (Carey, 1969), it was found that both anterior and posterior septal lesions led

increased water intake, but only the animals sustaining anterior septal damage would perform operant responses to obtain and consume excess water. Carey (1969) thus obtained results similar to those of Harvey and Hunt (1965) for animals with anterior septal lesions, but offered a different explanation. He suggested that lesions placed in the anterior septum result in two deficits, a slight increase in thirst and a slight tendency towards response perseveration. In the operant situation, these two deficits combine so that the septal animal responds more often and thus obtains more rewards on FR and FI schedules of reinforcement.

It appears, therefore, that some animals with damage to the septum will work harder than controls to obtain water and food rewards. At the present time, it is unclear whether this effect is because of increased thirst, due to an enhancement of the rewarding properties of reinforcers, or to response perseveration, or to some combination of these effects. In the future, experimenters should consider all of these possibilities and an attempt should be made to separate the various factors.

It should be noted that in all of the studies cited above, one-half to one hour daily testing sessions followed water or food deprivation. This sort of experi-

ntal design is, perhaps, more suitable for examining the warding properties of stimuli rather than the effects of e experimental treatment on motivation, particularly nce lesions of the septum disrupt affective processes nd behaviours (see below). Since the increased water take of rats with lesions of the septum is usually pressed as the percentage increase per 24 hours over e normal or pre-operative levels, investigation into e motivational aspects of excessive water intake should so employ 24 hour testing sessions with water available libitum. In this way, it could be determined whether not septal rats will actually work at operant tasks to tain as much excess water as they do in the home cage.

HER EFFECTS OF SEPTAL LESIONS AND STIMULATION

Much of the present interest in the septum was imulated by the demonstration of hyperemotionality and perirritability following septal lesions (Brady and auta, 1953). Brady and Nauta (1953) described their perimental animals as wild and irascible, and termed hese behaviours the "septal syndrome." The hyperemotionality was observed to decline spontaneously over a period of seven to 14 days after surgery, and the duration of the syndrome could be further shortened through extensive handline (Brady and Nauta, 1955). Wishart (1967)

wed however, that septal animals remain hyperemotional
periods of up to three months after surgery if main-
ned in social isolation. To date, there has been no
empt to correlate the changes in emotionality with the
erdipsia often observed after septal lesions. A high
relation would suggest a similar causative mechanism,
le no correlation, indicating independence of hyper-
sia and hyperemotionality, would suggest that these
behaviours are mediated by different pathways and mech-
sms.

Various parts of the septum have also been shown
support self-stimulation, with the medial septal region
wing the strongest effects. Of particular interest is
demonstration that rates of septal self-stimulation
highly correlated with the degree of food deprivation
ady, Boren, Conrad and Sidman, 1957; Olds, 1958),
ggesting that the septal region is directly influenced by,
may be part of, systems concerned with homeostasis.
ts generally press at lower rates for septal self-stimu-
tion than for lateral hypothalamic or medial forebrain
bundle self-stimulation (McIntire and Wright, 1965),
indicating that septal stimulation is not as reinforcing
as stimulation in hypothalamic regions. This is supported
by results showing that rats prefer to press for food when

...y (Routtenberg and Lindy, 1965), or for water when ...sty (Falk, 1961), rather than for septal stimulation.

Septal stimulation has been shown to have pro... effects on heart rate and blood pressure (Malmo, ...; Covian, Antunes-Rodriques and O'Flaherty, 1964), ...ducing both bradycardia (elicited from the lateral ...um), and tachycardia (elicited from the medial septum). ...ious other effects have also been reported during and ...lowing septal stimulation. These include respiratory ...wing (Covian et al., 1964), shivering (Stuart, Kawamura ... Hemingway, 1961), and vasoconstriction and piloerection ...dersson, 1957). Kaada (1951) showed that septal and ...b-callosal stimulation produces an inhibition of reflexive ...d cortically induced movements.

...E PRESENT STUDY

It is clear from the earlier sections that lesions ...f the septal area in the rat increase water intake. A ...ood deal remains to be learned, however, about the pheno... ...enon and the mechanisms of septal hyperdipsia.

The first part of the study was concerned with septal hyperdipsia immediately after the lesions were placed (Chapter 2) and several weeks after surgery, when the increased water intake had been stable for some time (Chapter 3). The experiment reported in Chapter 2 dealt

with the onset and time course of the hyperdipsia, whether the hyperdipsia preceded or followed the onset of polyuria, and the possible relationship of the hyperdipsia to the increased emotionality observed following septal lesions. In Chapter 3, the occurrence and patterning of drinking responses in the rat with septal lesions were recorded and compared with feeding responses. In Chapter 4, an operant technique was used to determine whether septal lesions which result in hyperdipsia also increase the drive to obtain water.

Since septal lesions did not increase the frequency of drinking, but resulted in longer bouts of drinking before water intake terminated (Chapter 3), and did not increase thirst drive as measured by an operant technique (Chapter 4), the second part of the study was concerned with the possibility that the septum is part of an inhibitory or satiety system for water intake. A direct test of this hypothesis was made by stimulating the septum with electric current (Chapter 5). Additional, indirect support for the hypothesis was provided in an experiment showing that septal hyperdipsia is influenced by food deprivation (Chapter 6). The final experiment, reported in Chapter 7, was undertaken to produce septal hyperdipsia in another species, the guinea pig, and to examine the locus of the

lesion responsible for hyperdipsia.

CHAPTER 2

The experiment reported in this chapter is concerned with the basic phenomena of septal hyperdipsia. The time course of hyperdipsia and polyuria in the rat following a septal lesion has not been adequately examined, although several experimenters have noted that polyuria usually occurs first and that hyperdipsia may develop several days after surgery (Wolfe, 1965; Lubar et al., 1969; Kasper-Pandi, Schoel and Sysman, 1969). Furthermore, the evidence concerning body weight changes and alterations in food intake is conflicting (Simmons and Thomas, 1961; Reynolds, 1962; Beatty and Schwartzbaum, 1967; Donovick and Burright, 1967, 1968; Lubar et al., 1969). Finally, although the interest in the septal area was originally stimulated by the observation of hyperemotionality following septal destruction (Brady and Nauta, 1953), there has been no attempt to relate the changes in affective behaviour with those found in consummatory behaviour.

In the present experiment, water intake, urine output, food intake and body weight were closely observed

during the initial recovery period following septal lesions. Similar observations were made for several months after surgery to determine the permanence of the effects. In addition, correlations were computed between the emotionality changes which occurred following the lesions with the degree of hyperdipsia observed.

METHOD

Subjects (Ss): The Ss were 30 male, black-hooded rats, all 4 mon. of age, and weighing 250 to 275 gm. at the time of surgery.

Apparatus: The rats were housed individually in wire mesh cages measuring 24 cm. long by 19 cm. wide by 16 cm. high, mounted in a cage rack. Each cage supported a urine-collecting funnel attached to the wire mesh floor. Fine wire screens were used to prevent feces and food pellets from dropping onto the collecting funnels. Urine was collected in a 50 ml. graduated cylinder positioned beneath the collecting funnel. Tap water was available in two 50 ml. graduated tubes (Fisher Scientific Co. Ltd.), fastened to the front of the cage. A supply of 45 mgm. food pellets (P.J. Noyes Co., Lancaster, Pa.) was available in a cup fastened to the front of the cage.

Procedure: Upon being received in the laboratory, the body weight of each S was recorded and the Ss were placed

in individual cages. Water and food intakes, urine outputs, and body weights were recorded daily for 2 wk. At the same time each day, the recordings were made and the urine and water bottles washed and replaced. The collecting funnels and wire screens were also cleaned and replaced daily.

After 2 wk., the animals were divided into 2 groups matched for water intake (ml. water per day per 100 gm. of body weight). The animals in the first group received sham operations which consisted of anaesthetizing the S, placing it in the stereotaxic, and making a scalp incision. Two holes were drilled, one on either side of the midline, anterior to bregma. Wound clips were then inserted, the animal removed from the stereotaxic, given an intramuscular injection of penicillin, and replaced in its cage.

The animals in the second group received septal lesions with co-ordinates: anterior 2.0 mm. to bregma, lateral 0.5 mm. on either side of the midline, and ventral 6.0 mm. from the surface of the skull. The incisor bar was set at +2.5 mm. The electrode was constructed of 28 gauge nichrome wire, insulated except for 0.5 mm. at the tip. A rectal cathode completed the circuit. The lesion parameters were 2.0 mA d.c. for 15 sec. The post-operative

treatment was the same for the control and experimental animals.

Observations were made of water and food intakes, and urine outputs at intervals of 1, 2, 4, 8, 12, and 24 hr. after surgery. These observations were then made daily for a period of 3, and in some cases, 4 mon.

On the 7th day after surgery, all Ss were rated by 3 independent observers on the 4 point scale of emotionality developed by Brady and Nauta (1953). On day 8, all Ss were tested in an open-field constructed of plywood, 122 cm. by 122 cm. by 30 cm. high, with the floor measured off into 30 cm. squares. Observations were made of the number of squares entered in a 10 min. session. Correlations were computed between the emotionality and activity scores and the measures of water intake.

At the completion of the experiments, all Ss with lesions of the septal area were sacrificed, and perfused through the heart with saline and 10% formal-saline. The brains were removed and stored in 10% formalin for 2 to 3 wk. Frozen sections were then made at 30μ and stained with thionin to permit histological verification of the lesions.

RESULTS

Only 11 of the 15 Ss which received lesions of the septum exhibited increased water intake post-operatively.

The increase in water intake averaged 18.3 ml. The greatest increase shown by a control S was 3.1 ml./day. The remaining experimental Ss showed only slight elevations in water intake which were within the range of increase by the Controls. The first group of experimental Ss were termed 'septal drinkers', and the second group was called 'septal nondrinkers'.

The development of hyperdipsia and polyuria as well as the measures of food intake and body weight are presented in Table 1. The control Ss remained anaesthetized for approximately 2 hr. after surgery, during which very little urine was collected. As the animals became aroused, more urine was excreted, although at the end of the first 24 hr. period following surgery, the urine output by the controls was slightly less than that during any comparable pre-operative period. Urine volumes were back to normal on the second day after surgery.

The septal animals of both groups remained anaesthetized for much longer periods than the controls (an average of 4 hr.), and most of these Ss began to excrete urine within 1 to 2 hr. after surgery. More urine was excreted by the septal drinkers than by the controls during the first post-operative day ($t=2.2$, $df=24$, $p < .05$, all tests two-tailed). A further increase in urine volume by the septal drinkers was noted on the second day after surgery; the elevated urine output by these Ss was observed throughout the entire post-operative period. The septal nondrinkers

TABLE 1

Effects of Septal Lesions on Water Intake, Urine Output, Food Intake and Body Weight During the Recovery Period After Surgery

	Time After Surgery (hr.)										
	0-1	0-2	0-4	0-8	0-12	0-24	24-48	48-72	72-96	96-120	120-144
Water Intake (ml.)											
Con	0	0	0	5.5	8.3	27.3	36.8	34.0	33.0	35.2	38.3
SN	0	0	0	2.1	4.4	23.2	40.1	42.3	40.4	43.4	44.1
SD	0	0	0.5	1.3	1.5	19.6	58.8	65.4	67.0	73.5	68.5
Urine Output (ml.)											
Con	0	0.3	2.3	5.8	8.5	14.5	17.3	15.5	15.0	16.2	16.8
SN	0.5	0.7	2.8	6.4	10.2	15.2	18.6	19.4	18.3	19.7	19.6
SD	1.1	1.8	3.1	9.0	14.0	18.5	31.4	37.3	38.0	38.2	36.4
Food Intake (gm.)											
Con	0	0	0	0	0	15.0	20.5	24.5	18.7	23.2	24.6
SN	0	0	0	0	0	13.0	20.3	16.9	19.5	20.0	21.1
SD	0	0	0	0	0	11.1	13.7	15.2	15.7	14.8	18.5
Body Weight (gm.)											
Con	258					257	261	260	262	263	263
SN	259					256	253	251	251	250	252
SD	261					258	254	248	243	240	241

tended to excrete more urine than the controls during the first post-operative day and during the subsequent recovery days, but the differences were not statistically significant (t=1.5, df=18, p>.20).

The water intake of the controls was depressed immediately after surgery, and slightly less water was consumed by the Ss in this group during the first 24 hr. recovery period. Water consumption returned to pre-operative levels on the second post-operative day. The water intake of the septal drinkers was even more depressed during the initial recovery period following surgery, presumably because of the longer period of recovery from the anaesthetic. The septal drinkers drank significantly less water than the controls during the first post-operative day (t=2.1, df=25, p<.05). Most of the septal drinkers began to drink excess water beginning on the second day after surgery, although in some Ss this did not occur for 3 or 4 days. Elevated water intake was then observed on all subsequent measuring periods (t=8.0, df=25, p<.001). The septal nondrinkers drank slightly less water than the controls during the first post-operative day. Starting on the second day after surgery, the septal nondrinkers tended to consume more water than the controls but this difference did not reach significance (t=1.1, df=18, p>.10).

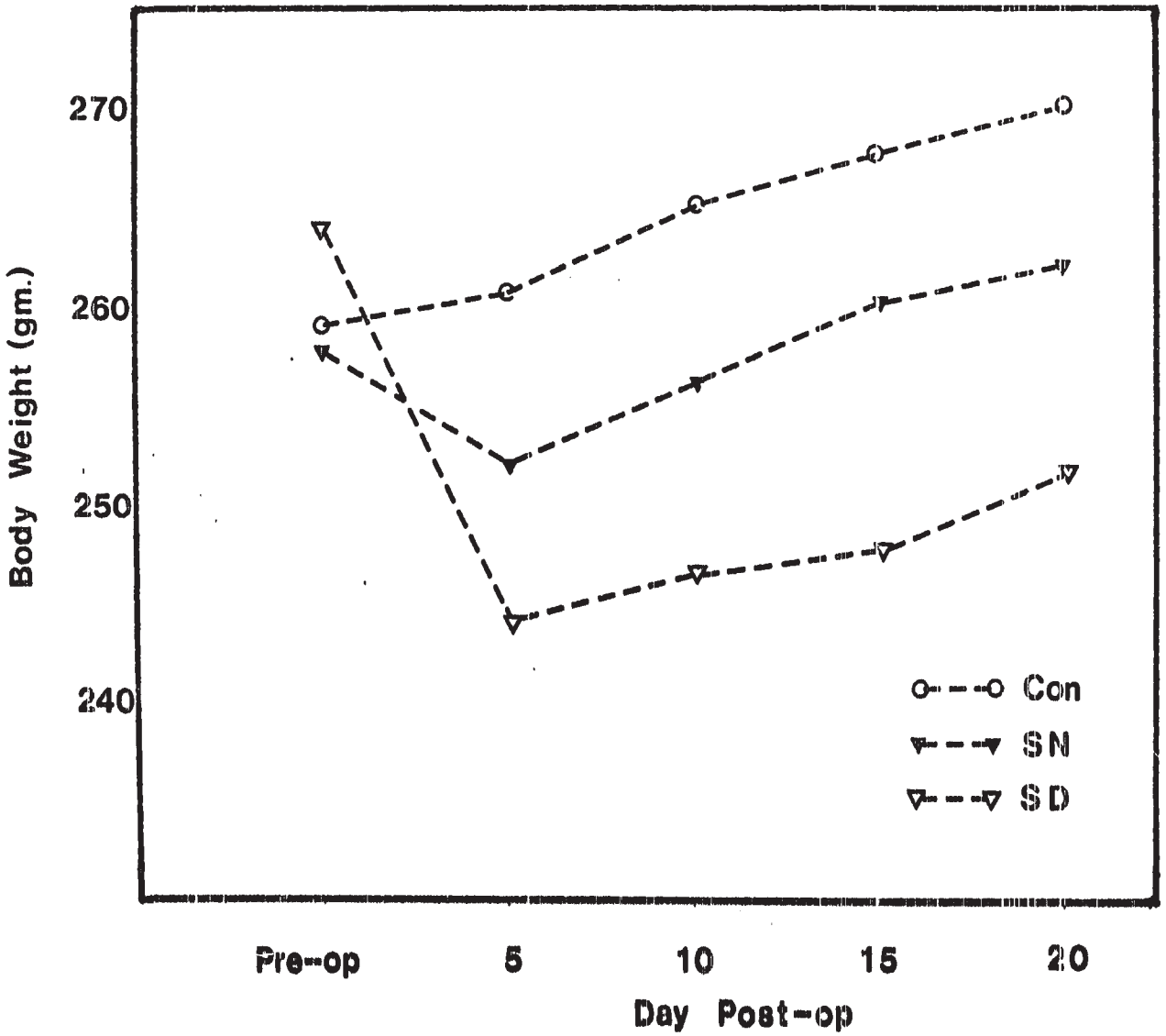
The Ss of all 3 groups consumed less food on the first day after surgery than pre-operatively, and the septal drinkers consumed significantly less than the controls on both the first and second post-operative days ($t=2.8$, $df=24$, $p<.01$). From day 2 to day 6, there were no differences between the groups in food consumption.

The Ss in all groups lost weight immediately after surgery (Fig. 1). The controls lost an average of 4 gm., the septal nondrinkers lost an average of 11 gm., and the septal drinkers lost an average of 21 gm. One wk. after surgery, the septal drinkers weighed significantly less than the controls ($t=2.2$, $df=24$, $p<.05$). There were no statistical differences between the septal drinkers and the septal nondrinkers ($t=1.6$, $df=13$, $p>.10$), or between the septal nondrinkers and the controls ($t=1.4$, $df=17$, $p>.10$).

In contrast to the septal drinkers in which an 'absolute' hyperdipsia was observed, the septal nondrinkers were found to be 'relatively' hyperdipsic. A slight loss of weight and a slight increase in water intake, neither of which was significant alone, combined to produce a significant increase in water intake when corrected for body weight ($t=2.34$, $df=17$, $p<.05$).

A comparison of the pre- and post-operative

Fig. 1. Mean body weights of controls (Con), septal nondrinkers (SN), and septal drinkers (SD) before and after surgery. The lesions were placed in the septal area on day 1.


270
260
250
240
Body Weight (gm.)
Con
SN
SD
Pre-op
5
10
15
20
Day Post-op

measures of water intake, food intake and body weight of the 3 groups is given in Table 2. The post-operative measurements were made 5 wk. after surgery. At that time, the septal drinkers weighed, on the average, 15.5 gm. less than the controls but drank more water ($t=6.7$, $df=24$, $p < .001$). The septal drinkers also tended to consume more food than the Ss of the other 2 groups, but this difference did not reach statistical significance ($t=1.1$, $df=28$, $p > .20$). Observations made 3, and in some cases 4. mon. post-operatively showed similar results.

The emotionality and activity scores, as well as the water intake data for each S, are presented in Table 3. A Kruskal-Wallis One-Way Analysis of Variance by Ranks was used to determine the significance of the differences among the groups for the emotionality and activity measures. The septal Ss of both groups scored higher on the emotionality scale than the controls ($H=12.6$, $df=2$, $p < .01$). The Ss in the 2 experimental groups were not different from each other in terms of emotionality. The control Ss were found to be the most active in the open field test, and the difference between these Ss and those of the 2 septal groups was highly significant ($H=10$, $df=2$, $p < .01$). Many of the septal animals of both groups were hypoactive in the open field. The septal drinkers did not differ from the septal nondrinkers in activity ($H=.10$, $df=2$, $p > .10$).

TABLE 2

A Comparison of the Pre- and Post-Operative Food and Water Intakes and Body Weights of Controls, Septal Drinkers and Nondrinkers.

Food Intake (gm.)

	N	Pre-Operative	Post-Operative
Con	15	23.1 ± 1.4	22.8 ± 1.7
SN	4	24.2 ± 1.6	23.6 ± 1.9
SD	11	23.7 ± 1.1	24.1 ± 2.1

Water Intake (ml.)

	Pre-Operative	Post-Operative
Con	35.7 ± 2.1	36.3 ± 1.9
SN	35.1 ± 1.7	41.1 ± 2.6
SD	36.3 ± 1.9	54.6 ± 4.2

Body Weight (gm.)

	Pre-Operative	Post-Operative
Con	259.1 ± 3.0	275.0 ± 4.4
SN	258.7 ± 3.6	267.4 ± 5.2
SD	261.6 ± 3.8	259.5 ± 6.6

Values are means ± standard deviations.

TABLE 3

Drinking, Emotionality and Activity Scores for the Controls, Septal Drinkers and Nondrinkers.

	S	Water Intake*	Emotionality	Activity
Con	60	10.2	7	39
	61	11.4	13	53
	62	9.8	8	127
	63	12.0	9	19
	64	12.2	11	20
	65	11.6	7	8
	66	10.4	12	74
	67	9.9	12	91
	68	10.8	14	86
	69	10.2	11	0
	70	12.1	9	19
	71	13.3	10	27
	72	12.7	12	153
	73	12.2	10	179
	74	10.4	7	102
	Mean	11.3	9.8	66.5
SN	80	13.3	13	1
	87	12.7	7	0
	89	12.9	26	0
	90	13.0	22	4
	Mean	13.0	17.0	1.2
SD	76	19.0	20	4
	77	19.1	8	0
	78	23.2	19	0
	79	17.8	24	71
	81	28.8	10	10
	82	19.7	19	0
	83	29.2	27	147
	84	13.6	7	4
	85	17.4	28	0
	86	23.2	21	15
	88	16.7	11	27
	Mean	20.9	17.6	25.3

* Values reported are means (ml./100 gm. body weight)

The correlations computed between the emotionality, activity and drinking data are presented in Table 4. There were no significant correlations between the hyperdipsia and hyperemotionality either immediately after surgery or several weeks after the operation. Furthermore, there were no significant correlations between the drinking and activity scores or between the activity and emotionality scores for any of the 3 groups. The only significant correlation obtained was that between the emotionality and drinking scores for the controls. Since this was a negative correlation, it indicates that the more emotional controls tended to consume less water.

A composite diagram of the lesion produced in a septal drinker is shown in Fig. 2. There did not appear to be any gross differences in lesion size or placement in the septal drinkers and nondrinkers. The average lesion tended to destroy most of the septum rostral to the anterior commissure, including the medial septal nucleus, the anterior portion of the lateral septal nucleus, the superior fornix and the dorsal diagonal band region.

DISCUSSION

The results of experiment 1 indicate that polyuria develops prior to hyperdipsia following a septal lesion. Urine was excreted during the anaesthetic state, and output

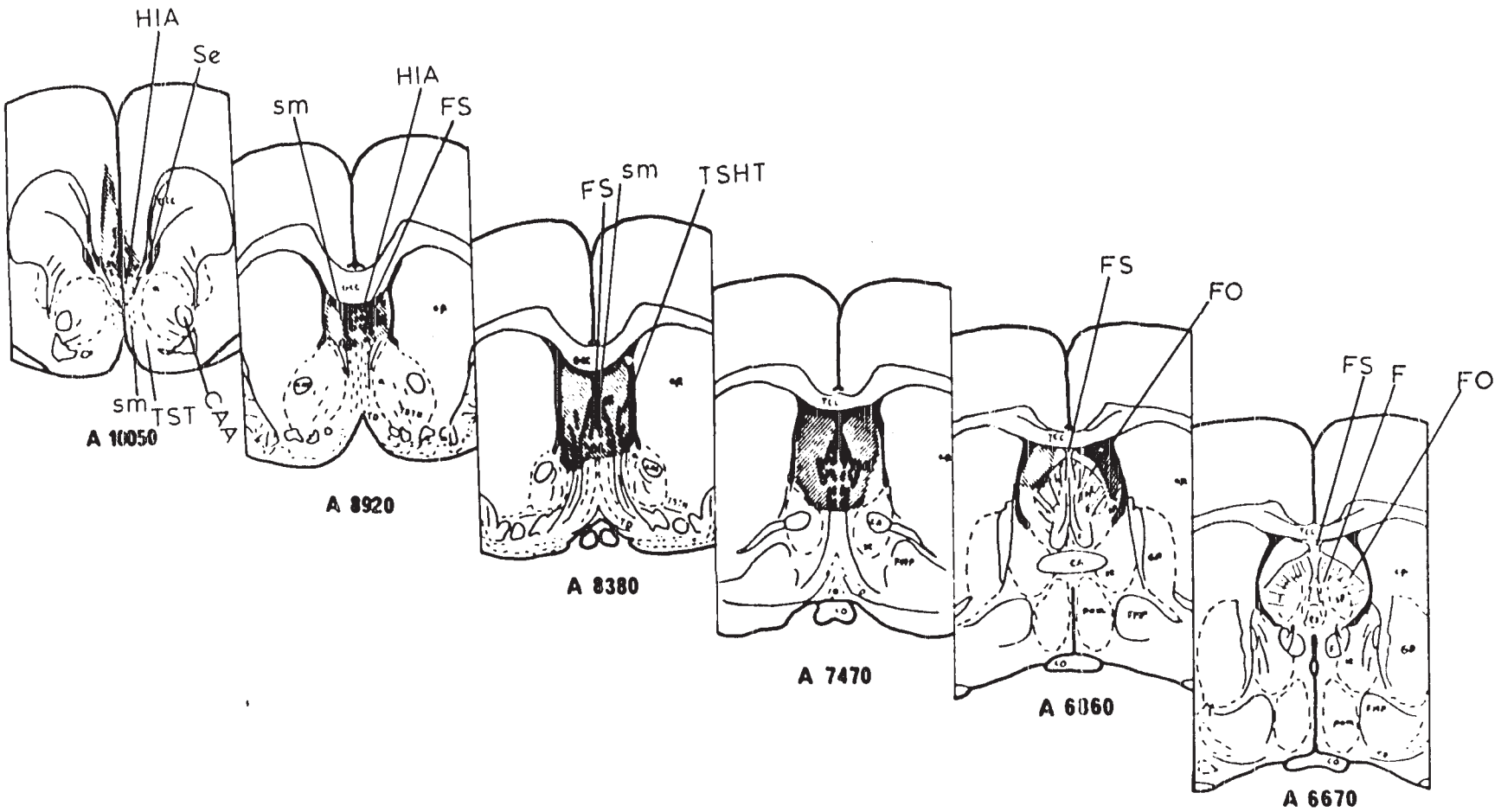
TABLE 4

Spearman Rank-Order Correlations Obtained Between Water Intakes and Emotionality and Activity Scores

	Water Intake and Emotionality	Water Intake and Activity	Activity and Emotionality
Con	-.82*	.31	-.08
SN	.50	.35	.35
SD	.19	.22	.12

* Significant at .05 level

Fig. 2. A reconstruction of the lesion produced in a septal drinker. List of abbreviations: a, nucleus accumbens septi; ca, anterior commissure; co, optic chiasm; cp, caudate-putamen; F, fornix; FS, superior fornix; GCC, genu corpus callosum; GP, globus pallidus; HIA, hippocampus, pars anterior; sf, nucleus septo-fimbrialis; sl, nucleus septalis lateralis; sm, nucleus septalis medialis; pom, nucleus preopticus medialis; TCC, corpus callosum; td, nucleus of the diagonal band of Broca; TD, diagonal band; st, nucleus septalis triangularis; TSTH, septal-hypothalamic tract.


HIA
Se
sm
TST
CA
A 10050
sm
HIA
FS
A 8920
FS
sm
TSHT
A 8380
A 7470
FS
FO
A 6060
FS
F
FO
A 6670

exceeded intake during the first 12 hr. These observations are in agreement with those of Wolfe (1965) and Lubar et al. (1968), who also found that the polyuria of septal animals developed before hyperdipsia.

Increased water intake did not begin until the second day after surgery, and in some animals, it did not occur until the fourth post-operative day. The hyperdipsia developed gradually over 2 or 3 days before water intake levelled off. Similar observations were reported by other investigators (Kasper-Pandi et al., 1969; Lubar et al., 1969).

The initial decrease in food consumption of the septal drinkers was reflected in a loss, on the average, of 20 gm. of body weight during the first week after surgery. Similar results were reported by Beatty and Schwartzbaum (1967). Some of this weight loss may also be attributed to the initial polyuria which was not accompanied by hyperdipsia until the second post-operative day. There is no evidence that increased activity, which might account for some weight loss, occurs after septal destruction. In fact, as reported earlier by Douglas and Raphaelson (1966), for the open field, septal animals in the present study tended to be hypoactive in most situations.

The tendency of the septal drinkers to consume

more food following the initial depression of food intake may have occurred for two reasons. Since food and water intakes are intimately related (Cizek, 1961), the increase of water intake may have resulted in a corresponding increase in food intake. Second, most animals find the pellets used in the present study very rewarding and prefer them to normal lab chow pellets. Since septal animals overreact to the taste properties of food (Beatty and Schwartzbaum, 1967, 1968), the septal animals may have eaten more food for this reason.

Of interest is the observation that some animals with septal lesions that do not show an absolute hyperdipsia, do consume more water than controls when adjusted for differences in body weight. This 'relative' hyperdipsia, previously reported by Beatty and Schwartzbaum (1967) has not been explained. It may be related to the locus or amount of damage to the septum, but a comparison of the histological sections of the brains of the septal drinkers and nondrinkers did not reveal any gross differences.

Although Harvey and Hunt (1965) reported that septal animals remain hyperdipsic for up to seven months after surgery, Beatty and Schwartzbaum (1967) found that the intake of rats with septal lesions declined from a peak

intake (which occurred about 4 days after surgery), until there were no differences in water intake between the septal and control animals. Other studies (Wolfe, Lubar and Ison, 1967; Lubar et al., 1968) have reported a similar decline, although significant differences continued to exist for at least two weeks after surgery. In the present experiment, the septal drinkers were hyperdipsic until they were sacrificed, in some cases four months after surgery. Some animals showed a slight decline in water intake, but in others this did not occur. This difference may also be related to the amount of damage to the critical structures of the septum responsible for the hyperdipsia, since those animals which showed no decrease in water intake were those which suffered the most extensive damage to septal structures. Some recovery may be possible when incomplete destruction of this area occurs.

The septal animals (both drinkers and nondrinkers), were found to be, on the average, more emotional and less active than normal controls. These findings confirm the results of earlier studies (Brady and Nauta, 1953; King, 1958; Douglas and Raphaelson, 1966). However, in the present experiment, no consistent relationship between hyperdipsia and hyperemotionality was evident, and this may suggest that these two behaviours are unrelated. Further-

more, although the hyperemotionality and hyperirritability dissipate after a week or two, especially with handling and social interaction (Brady and Nauta, 1955; Wishart, 1967), the increase in water intake is permanent. Thus the effect of septal lesions on emotionality is unrelated to the effect of such lesions on water intake, and apparently, the two are subserved by different mechanisms.

The fact that polyuria has an earlier onset than hyperdipsia led Lubar and his associates (1969) to suggest initially that the hyperdipsia is secondary to a primary loss of water from the body as urine. As indicated in the introduction, however, subsequent work showed that this was not so and that septal lesions result in primary hyperdipsia (Lubar et al., 1968). Thus, the increased water intake of septal rats, although preceded and perhaps initiated by the loss of excessive water from the body as urine, appears to be independent of increased urine output. As shown by Harvey and Hunt (1965), the hyperdipsia does not appear to be related to increased food intake either.

Another possibility is that the hyperdipsia from septal lesions is the result of increased thirst drive (Harvey and Hunt, 1965). Although this hypothesis warrants serious attention, the results reported in Chapter 4, as well as results of other investigations, do not support this

interpretation.

CHAPTER 3

The first experiment dealt mainly with the temporal course of hyperdipsia from septal lesions during the first few days after surgery. The second experiment went on to consider the pattern and characteristics of drinking in the septal rat several weeks after surgery, when water intake was stable.

In order to record more precisely consummatory behaviour, rats were trained to press a lever to obtain food. Drinking was recorded by means of a drinkometer relay. The occurrence and pattern of responses for food and water of rats with septal lesions were recorded and compared to those of control rats during continuous tests of 24 hours duration, and for two hour periods following 22 hours of water deprivation.

METHOD

Subjects (Ss): The Ss were 20 male, black-hooded rats, each 3 mon. of age and weighing 250 to 275 gm.

Apparatus: The apparatus for the first part of the experiment consisted of 2 modified Skinner boxes (Ralph Gerbrands Co. Ltd., Model D1). The sides and tops of the boxes were of clear plexiglass, and the floor of steel rods. A lever was mounted 8 cm. above the grid floor at one end of the box. A response on this lever led to delivery of a 45 mgm. food pellet to a food cup located below and to the left of the lever. A water spout protruded into the cage on the side opposite to the lever. Laps at the spout activated the drinkometer, and were recorded on a counter. Each lap also caused a deflection of a pen on an event recorder (Esterline Angus Recorder, Model 6207). Responses on the food lever were also both counted and recorded on the event recorder.

PROCEDURE: The Ss were divided into 2 groups, matched for water intake (ml. water per day per 100 gm. body weight). The Ss in the first group received sham operations while those in the second group received lesions as described in Chapter 2. There was a 1 wk. recovery period before testing began. Following testing, the animals were sacrificed and their brains obtained. A histological procedure similar to that following the first experiment was carried out.

Following the recovery period, each S was, in

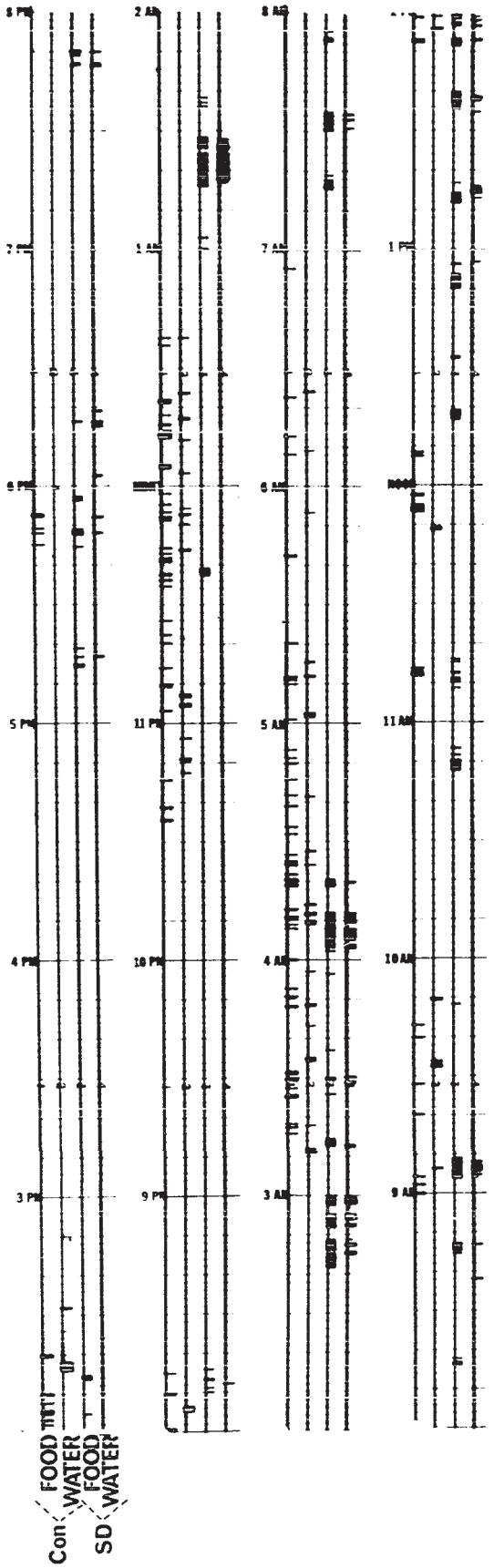
turn, deprived of food and placed in one of the operant boxes to learn to depress the lever to obtain food reward. All the Ss learned this response rapidly without shaping, and the deprivation was discontinued. Testing was carried out when the Ss were sated for food and water. They were tested in pairs, a control and a septal drinker, for sessions of 24 hr. duration on a 12 hr. light-dark cycle (8 p.m. to 8 a. m.). Each S was tested 5 times with a 5-day intertrial interval. Records were made of the responses on the food lever, the number of laps at the water spout, and the quantity of water consumed (determined by weighing the water bottle each day). The records were analyzed to determine the differences, if any, in ingestion patterns between the septal and control animals.

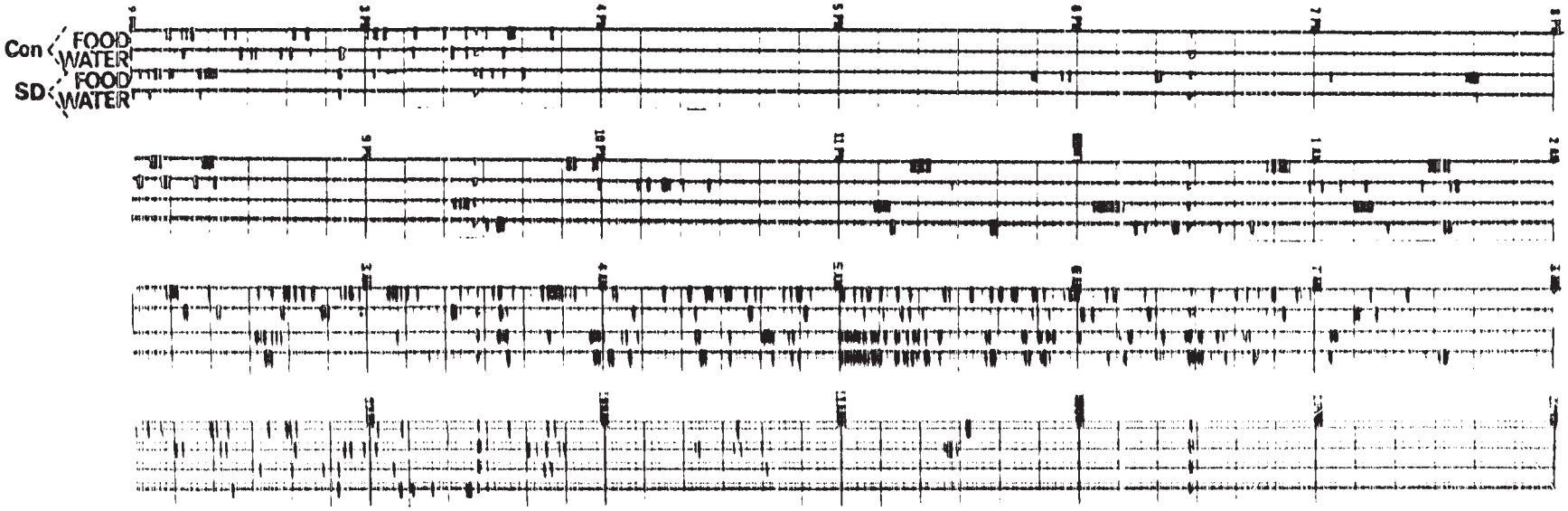
The Ss were then placed on a 22 hr. water-deprivation schedule with food available ad lib. Water was available to each S for the remaining 2 hr. of each day, and observations made every 1/2 hr. on the volume of water consumed by each S. The intakes for the 2 groups were compared for the 1/2 hr. periods.

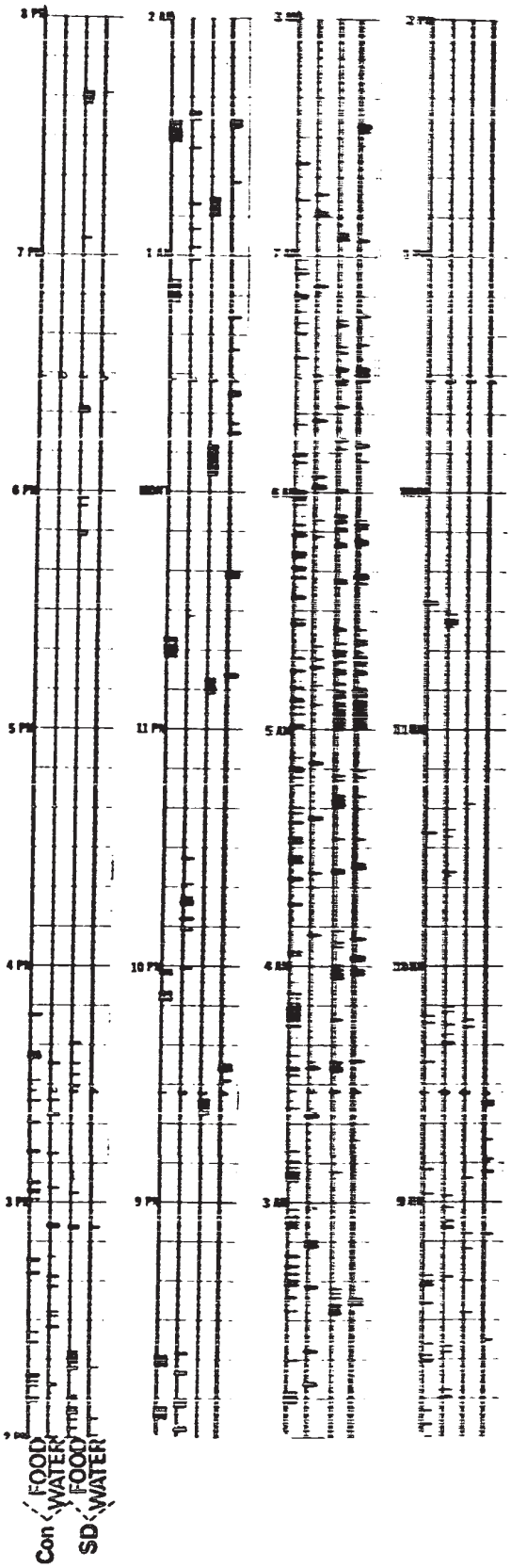
RESULTS

Two examples of the records made of the responses for water and food during a 24 hr. period by both septal and control Ss are shown in Figs. 3 and 4. The records indicate that while sporadic feeding and drinking occurred

Fig. 3. A continuous 24 hour record of the feeding and drinking of a control (Con) and a septal drinker (SD).


Con
FOOD
WATER
SD
FOOD
WATER


Con
FOOD
WATER
SD
FOOD
WATER


Con
FOOD
WATER
SD
FOOD
WATER

throughout the day, most of the consummatory behaviour of both the septal and control Ss was concentrated between 2 and 8 a.m. (during the dark cycle). Like the controls, the septal animals tended to drink shortly before or shortly after feeding. On only a few occasions did one consummatory activity occur without being in close temporal proximity to the other.

The most striking difference between the records for the septal and control animals was in the amount of time which the septal animals engaged in drinking. Although the frequency of drinking did not appear to be changed, as both the control and septal Ss initiated drinking 50 to 60 times per day, the number of laps at the water spout during a drinking bout was greately enhanced by a septal lesion ($t=11.2$, $df=18$, $p<.01$). The average amount of water consumed by the septal Ss was also significantly greater than that of the controls ($t=14.9$, $df=18$, $p<.01$). In contrast, the average number of responses for food made by the Ss of the 2 groups did not differ ($t=1.3$, $df=18$, $p>.20$). These data (water intake, laps at the water spout, and responses for food) are presented in Table 5.

Following the 22 hr. period of water deprivation, both the control and septal Ss began to drink immediately. The controls drank continuously for 15 to 20 min. before pauses were noted. After the first 1/2 hr. of access to

TABLE 5

Average Water Intake, Mean Number of Laps at the Water Spout, and Responses on the Food Lever by Controls and by Septal Drinkers

	Water Intake (ml.)
Con	32.8 ± 2.1
SD	62.5 ± 5.9
	Laps at the Water Spout
Con	3993 ± 540
SD	7509 ± 834
	Responses for Food
Con	504 ± 107
SD	568 ± 104

Values are means ± standard deviations.

water, these Ss approached the water spout intermittently and drank only for very brief periods. The septal Ss, however, continued to drink continuously for much longer periods of time (from 20 to 40 min. after being allowed access to water). Thereafter, the ingestion pattern of the septal Ss was similar to that of the controls.

These behavioural differences were reflected in the different volumes of water consumed by the animals of the 2 groups (Table 6). There were no differences in water intake between the control and septal Ss during the first ($t=.3$, $df=18$, $p>.10$), or last ($t=1.9$, $df=18$, $p>.05$) 1/2 hr. periods, but the average volume of water consumed by the septal animals was significantly greater than that of the controls during the second ($t=18.3$, $df=18$, $p<.01$), and third ($t=5.1$, $df=18$, $p<.02$) 1/2 hr. periods.

DISCUSSION

The results obtained in the first part of the experiment suggest that the septal animals do not drink any more often than controls, nor is the cyclic-diurnal pattern of drinking altered after a septal lesion. Rather, once drinking was initiated, the septal animals engaged in longer bouts. Similar observations were made by Blass and Hanson (1970). They observed that, as in the normal rat, drinking in the septal rat occurred either before or after

TABLE 6

Water Intake of Control and Septal Rats Following

24 Hours of Water Deprivation

	Water Intake (ml.)				
	0-30 min.	30-60 min.	60-90 min.	90-120 min.	Total
Con	16.6 ± 1.5	3.4 ± 1.1	1.8 ± 0.9	1.1 ± 0.5	22.9 ± 1.8
SD	16.8 ± 1.7	6.7 ± 1.4	3.4 ± 1.3	1.5 ± 0.8	28.4 ± 2.0
Diff.	0.2	3.3*	1.6*	0.4	5.5*

*Significant at .05 level

Values are means ± standard deviations.

a meal, but that once drinking began, the "draughts were long and copious" (p. 89). Also, following the delivery of a dry food pellet, animals with septal damage were observed to engage in long bouts of drinking (Blass and Hanson, 1970). The results of the second part of the experiment confirm and extend these observations. While control animals ceased continuous drinking about 20 minutes after the initiation of drinking, septal animals continued for an additional 20 to 40 minutes. Donovick and Burright (1968) found that following two days of water deprivation, septal animals did not consume more water than controls during the initial 20 minutes of drinking. However, the septal rats continued to drink at elevated rates while the controls slowed down. After one hour, there was a significant difference in water intake. In summary, it appears that septal lesions do not alter either the rate of frequency of drinking, but do prolong the act of drinking once it has been initiated.

Chew (1965) reported that absorption of a water load in the rat begins immediately and is probably complete in about 35 minutes. Presumably, the normal rat utilizes and integrates some signal that water is being ingested (Oatley, 1967), since the rate of drinking slows down before the water is completely absorbed. That the rat

monitors water intake was shown by Epstein (1960). Rats were taught to press levers to obtain water which was delivered directly to the stomach through indwelling gastric tubes. The water intakes of these animals were usually greater than when they were allowed to drink normally. If the injected volume was increased, these animals did not adjust very rapidly, suggesting the loss of an immediate feedback response. Licking, tasting, swallowing and gastric distension probably all play a part in the metering process.

Since the cessation of drinking comes much later in the septal rat than in normal controls, this may reflect an inability to utilize the signals of water intake. The septal rat does eventually slow down and temporarily stop drinking, and this is probably due to the long-term satiety effects of water intake (i.e., a reversal of the conditions which originally initiated drinking). Thus, septal hyperdipsia appears to be related to a deficit in utilizing and/or responding to the short-term satiety signals for water intake.

CHAPTER 4

As indicated earlier, Harvey and Hunt (1965) originally suggested that increased water intake followed lesions of the septum due to increased thirst. A good deal of attention has been given to this suggestion, but definitive support is still lacking (Lubar et al., 1968).

The experiment reported in this chapter was undertaken to determine whether rats, hyperdipsic from septal lesions, will drink excessively when they have to perform a lever pressing response to obtain water. The rationale was that if septal rats increase water intake because of increased thirst drive, they should work to obtain it. To rule other interpretations such as response perseveration effects of septal lesions (McCleary, 1961), they were also allowed to press a lever for food.

METHOD

Subjects (Ss): The Ss were 24 male, black-hooded rats, 200 to 225 gm. and approximately 3 mon. of age at the time of surgery.

Apparatus: The experiments were conducted in 2 operant testing boxes. The first box was constructed of plexiglass painted flat-black, with a grid floor, and which measured 23 cm. long by 22 cm. wide by 21 cm. high. A lever was mounted 7 cm. above the floor at one end of the box. Responses on this lever led to delivery of 45 mgm. Noyes food pellets to a food cup located just below and to the left of the lever. A second lever, located at the opposite end of the box, was placed 6 cm. above the grid floor. A response on this lever was reinforced by delivery of 0.10 ml. of water by a liquid pump (Davis Scientific Instruments, Model No. LR-131A) to a plastic container fastened to the wall below and to the right of the lever. Responses on the 2 levers were recorded on counters, and the ratio of responses to reinforcements on either lever were varied by means of a schedule selector (BRS Electronics, M-SP, model 2901).

The second box measured 33 cm. long by 21 cm. wide by 30 cm. high, and was also constructed of plexiglass painted flat-black. One side of the box held a lever located 6 cm. above the grid floor. Responses on this lever were reinforced by access to a .10 ml. water cup which was raised into the box for a period of 3 sec. Again, the response to reinforcement ratio could be varied as described above. At the opposite end of the box was a tin cup

in which was placed a supply of 45 mgm. Noyes food pellets.

Procedure: One-half of the Ss received electrolytic lesions of the septal area as described in Experiment 1, designed to produce increased post-operative water intake. The remaining Ss received sham operations. A 1 wk. recovery period was allowed before testing began. With the exception noted below, the Ss were maintained on an ad libitum feeding and drinking schedule in their home cages during the first part of the experiment. Water and food consumption were measured daily during the 1 wk. recovery period, and at 1 wk. intervals thereafter.

Following the recovery period, each S received several days of pretraining in Box 1. The S was simply placed in the box and allowed several days in which to learn to press the levers to obtain the appropriate rewards. All of the Ss learned to make the responses required in both boxes.

Following the pre-training sessions, all of the Ss were placed on a 23 hr. water deprivation schedule and allowed 1 wk. to adjust to the new regimen. Each S was then tested for 1/2 hr. daily in Box 2, and the number of responses on the water lever during the session was recorded. The reinforcement schedule included FR1, FR5, FR10, FR15, and FR20 ratios, which were varied randomly for each

S. Each animal was tested 3 times under each reinforcement schedule, with a 1 day interval between sessions. Each S was allowed free access to water in the home cage for 1/2 hr. after each test.

The Ss were then tested in Box 1 following 23 hr. of food deprivation. The daily testing sessions lasted for 1/2 hr., and the animals were fed wet mash in the home cages for 1/2 hr. after each test. Similar reinforcement schedules were employed as in the water deprivation experiment.

Following the completion of part 1, the Ss were retested in Box 1, with testing sessions of 24 hr. duration. The S obtained food and water during the session by responding on the appropriate levers. The ratio of responses to reinforcements on the water lever was randomly varied for each S, and included FR1, FR2, FR4, FR5, FR10, FR15, and FR20 schedules of reinforcement. The number of responses, the number of reinforcements, and the volume of water obtained were recorded at the end of the 24 hr. period. Each S was tested 3 times under each reinforcement schedule, with an intertrial interval of 12 days.

RESULTS

The results obtained when the Ss were 23 hr. water deprived and required to lever press for water are

presented in Fig. 5. An analysis of variance performed on these data (Summary Table 1, Appendix A), showed that the animals with septal lesions responded more often than controls on FR1, FR5, FR10 and FR15 schedules of reinforcement ($p<.05$). There were no differences between the 2 groups on the FR20 schedule ($p>.05$).

The results obtained when the Ss were food deprived and permitted to respond for 45 mgm. food pellets are presented in Fig. 6. The analysis of variance performed on these data (Summary Table 2, Appendix A) showed that the rats with septal lesions responded for food more often than the controls on FR1, FR5, and FR10 schedules of reinforcement ($p<.05$). There were no differences when the animals were required to respond 15 or 20 times for each reward ($p>.10$).

Finally, the results obtained when the Ss were required to work for their total daily water are presented in Fig. 7. In the home cage, the control Ss drank a relatively constant amount each day (approximately 30 ml.). When placed in the operant situation and required to press up to 20 times for 1 reinforcement, the control Ss continued to obtain and drink approximately 30 ml. of water. In marked contrast, the rats with septal lesions consumed excessive amounts of water in the home cage, but in the

Fig. 5. Mean number of responses for water reinforcement under various schedules by controls (Con) and septal drinkers (SD) during 1/2 hour tests following 23 hours of water deprivation.

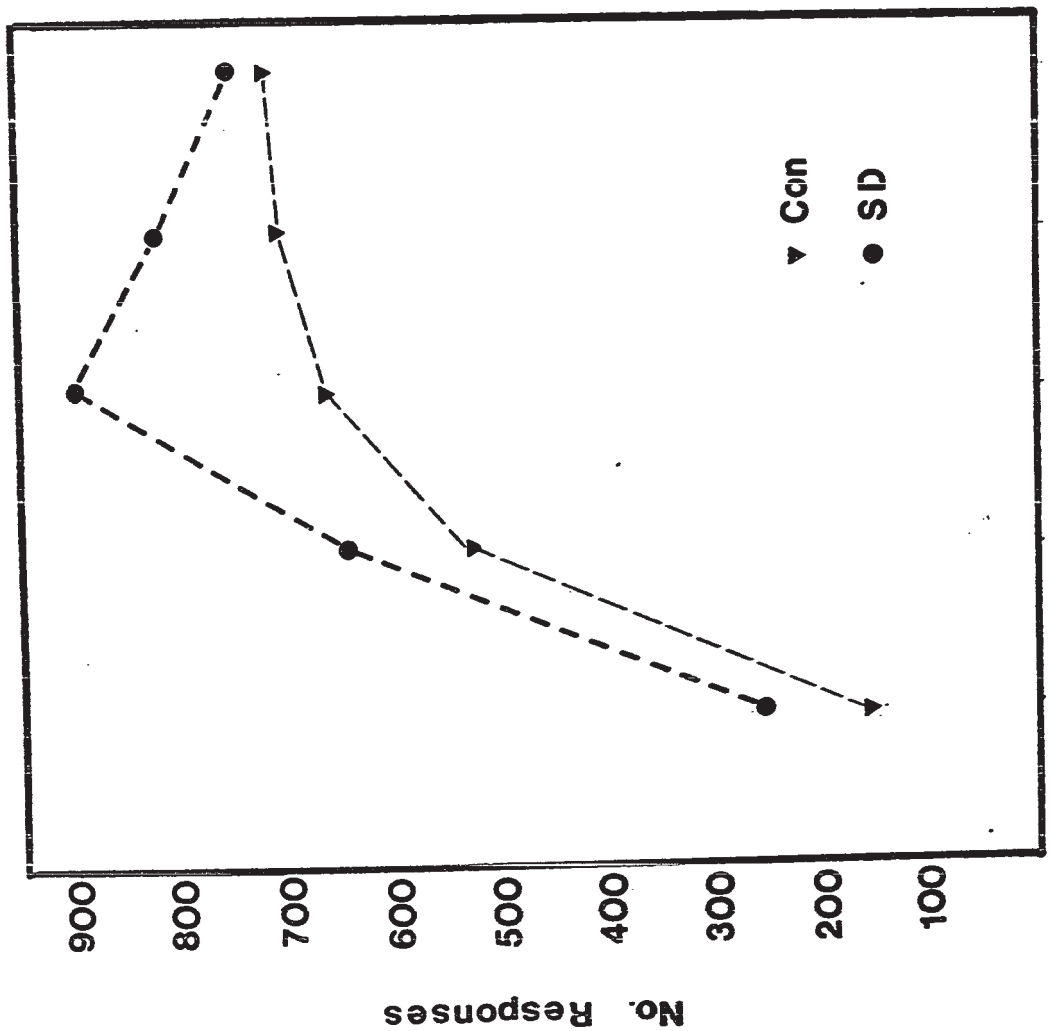

No. Responses
900
800
700
600
500
400
300
200
100
Con
SD
FR1
FR5
FR10
FR15
FR20
Reinforcement Schedule

Fig. 6. Mean number of responses for food reinforcement under various schedules by controls (Con) and septal drinkers (SD) during 1/2 hour tests following 23 hours of food deprivation.

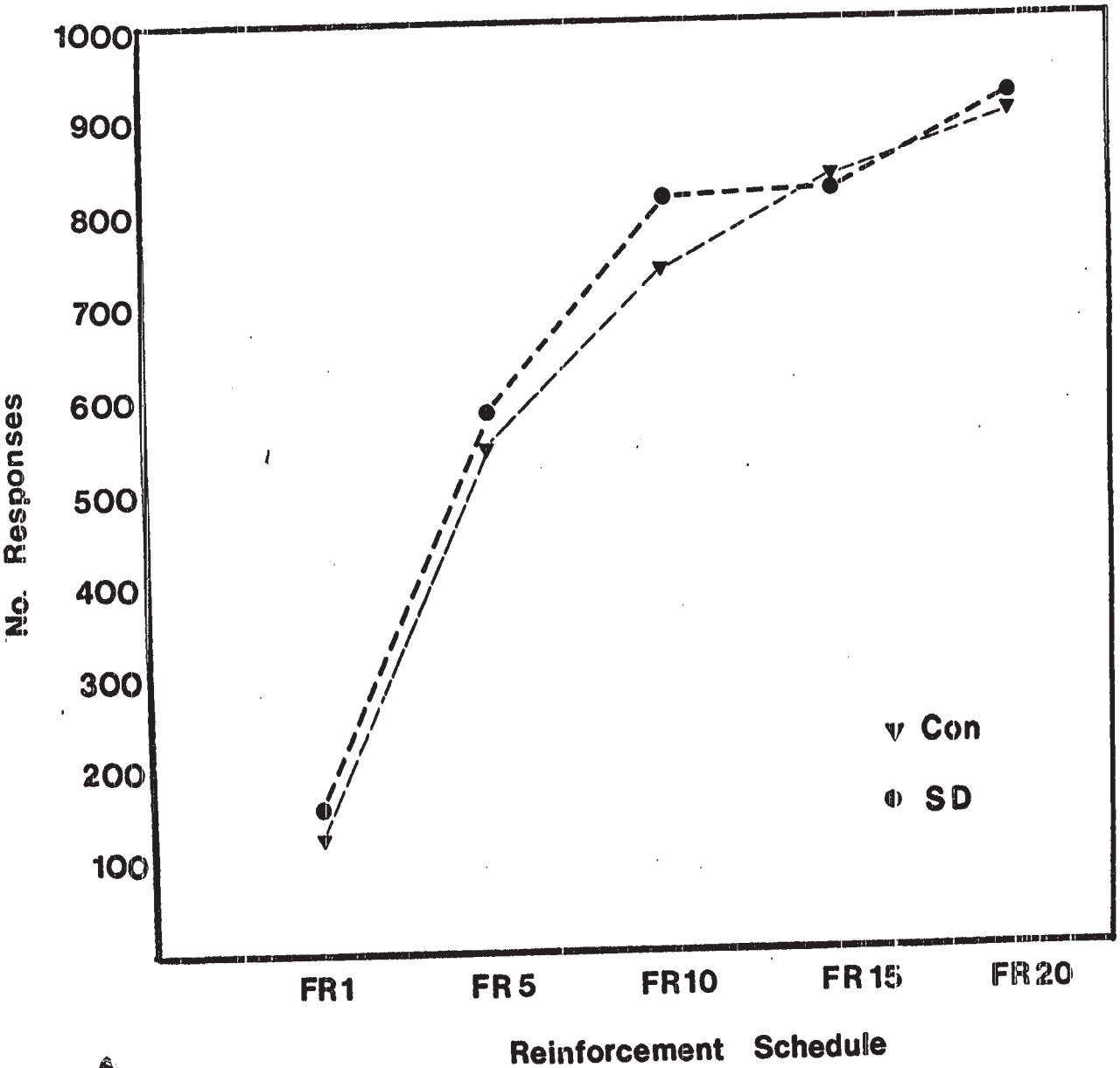
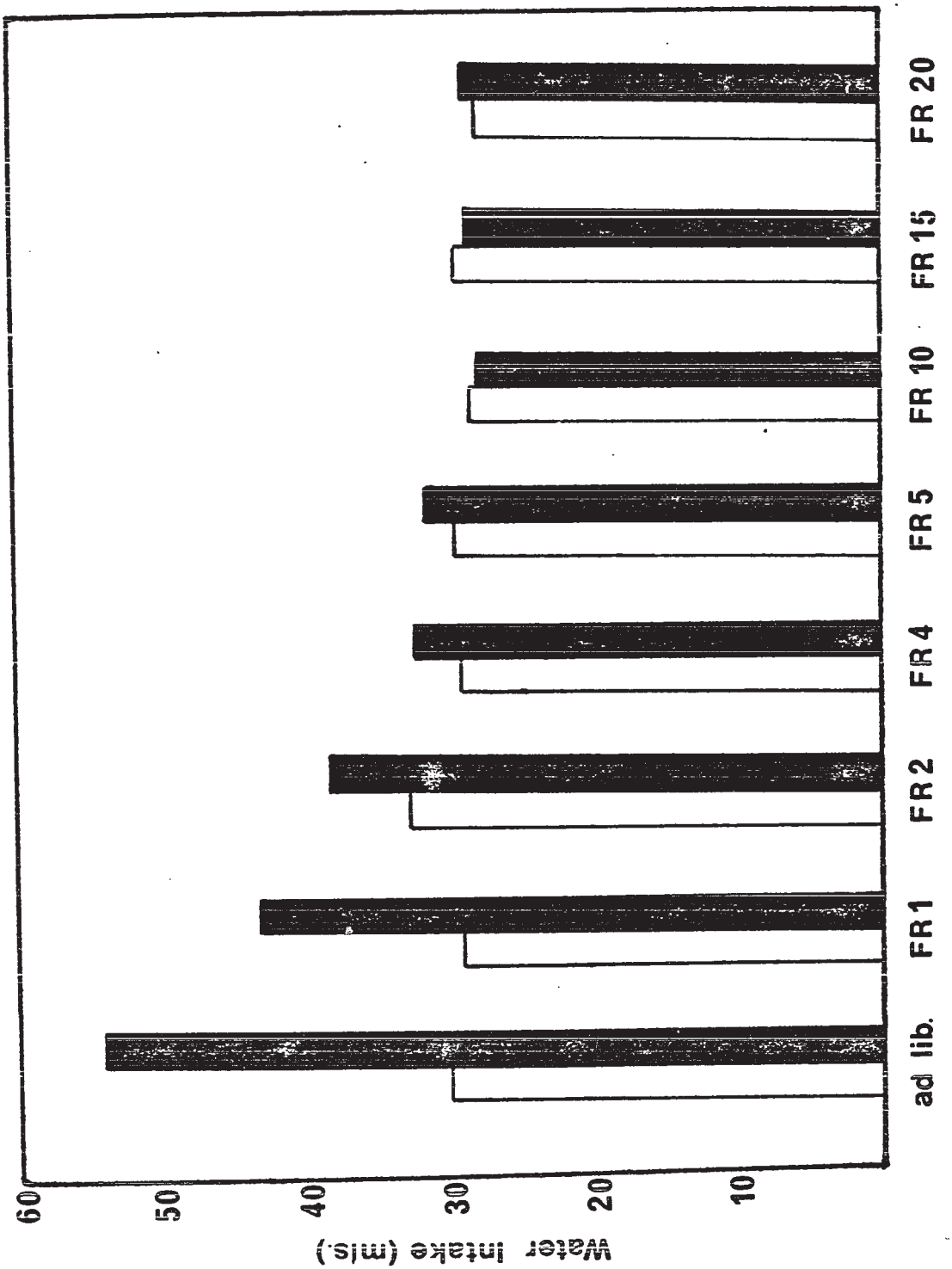

1000
900
800
700
600
500
400
300
200
100
No. Responses
v Con
o SD
FR1
FR5
FR10
FR15
FR20
Reinforcement Schedule

Fig. 7. Mean water intake of controls (open bars) and septal drinkers (filled bars) under ad lib. conditions, and during 24 hour tests in the operant situation. Water available continuously.


Water intake (mls.)
60
50
40
30
20
10
ad lib.
FR 1
FR 2
FR 4
FR 5
FR 10
FR 15
FR 20
Reinforcement Schedule

operant situation, obtained less and less water as the ratio of responses to reinforcements was increased up to FR10. Thereafter, the volume of water intake by the septal rats remained relatively constant, and no different from that ingested by the controls. An analysis of variance performed on these data (Summary Table 3, Appendix A) indicated a significant lesion effect, a significant schedule effect, and a significant interaction. Thus, the septal animals consumed more water than did the controls in the home cage and on the FR1, FR2, FR4 and FR5 schedules ($p<.05$). However, on the FR10, FR15 and FR20 schedules of reinforcement, the rats with septal lesions did not make more responses, and therefore did not obtain any more water than the controls ($p>.05$).

The average amount of food consumed by the Ss of the 2 groups in the home cage and in the operant situation (FR1), when on an ad libitum feeding schedule is shown in Table 7. The Ss in the lesion group did not differ from the controls in food consumption whether in the home cage or when lever pressing for food on an FR1 schedule ($t=1.6$, $p>.10$).

DISCUSSION

Rats with septal lesions drank more water than controls in the home cage with water available ad libitum.

TABLE 7

Ad Libitum Food Intake of Controls and Septal Drinkers In the Home Cage and In the Operant Situation on FR1

	Food Intake (gm.)	
	Home Cage	Operant FR1
Con	22.3 ± 1.4	21.8 ± 3.4
SD	24.1 ± 2.2	21.6 ± 2.9

Values reported are means ± standard deviations

This is consistent with the results of the experiments reported in Chapters 1 and 2. When the septal rats had to obtain water by pressing a lever continuously available during a 24 hr. period, they also showed increased water intake on the low FR schedules. As the reinforcement ratio increased, however, the hyperdipsia became less and with FR10, FR15, and FR20 schedules, the water intake of the septal rats did not differ from that of the controls. It appears that although rats with septal lesions drink more water when it is readily available, they do not work to obtain the excessive intake. This is reminiscent of the effects of lesions of the ventro-medial hypothalamus on food intake (Miller, Bailey and Stevenson, 1950), and suggests that the increased water intake in septal rats, like the increased food intake of VMH rats is due to the disruption of an inhibitory or satiety system.

Rats with septal lesions did not increase food intake either when food was available ad libitum in the home cage or when they lever pressed for food during a 24 hour period. This agrees with previous findings (Kasper-Pandi et al., 1969; Lorens and Kondo, 1969; Lubar et al., 1969), and it is not necessary to consider further, therefore, whether septal lesions increase hunger drive.

Deprivation seems to alter the usual operant

responding of septal rats to obtain food and water. With FR1, FR5, and FR10 schedules, they responded more than controls with water and food as the rewards for lever pressing. This could be response perseveration (McCleary, 1961; Burkett and Bunnell, 1966), but this is unlikely since response perseveration did not occur when food was the reward in the 24 hour sessions. Another possibility is that deprivation of rats with septal lesions enhances the reactivity to incentive conditions. This hypothesis was suggested originally by Ellen and Powell (1962), who observed that on FI schedules, septal animals exhibit high rates of bar pressing in the period immediately preceding a reinforcement. Ellen and Powell (1962) proposed that this behaviour is related to the anticipation of reward. A similar hypothesis was advanced by Zucker (1965) who suggested that the normal function of the septal area is to dampen the increase in response strength which normally follows a reinforcement.

Observations supporting this hypothesis have come from a number of different sources. Beatty and Schwartzbaum (1967) reported enhanced reactivity to both sucrose and quinine solutions following septal destruction. Buckland and Schwartzbaum (1970) found increased response rates on FR schedules for sucrose reward following septal damage.

Indirect support was provided in other studies. Lorens (1966) showed that septal lesions enhance response rates for lateral hypothalamic electrical stimulation, and Keesey and Powley (1968) reported that the thresholds for lateral hypothalamic self-stimulation decreased following septal destruction.

Harvey and Hunt (1965) showed that normal animals respond more frequently and more rapidly for water reward when 48 hours water deprived than when only 24 hours water deprived. Thus, if the septal animals are more thirsty than controls, they should respond more often than controls for water reward. During the 24 hour tests, the septal animals of the present experiment showed elevated rates of responding on the low FR schedules, possibly reflecting a slight increase in thirst as suggested by Carey (1969). However, the same animals would not perform on high FR schedules to obtain excess water. Since Carey (1969) found that rats with septal lesions show no impairment in responding on high FR schedules (up to FR80), the results of the present study do not seem attributable to a lesion effect on emotionality or motor behaviour which would disrupt rapid responding. More research is required employing operant techniques and a fine analysis of the responding patterns of septal animals is needed, but the results of the 24 hour tests are consistent with the suggestion that septal lesions increase thirst only slightly (Carey, 1969).

CHAPTER 5

It appears unlikely that the increased water intake which results from lesions of the septum is due to increased thirst (see Chapter 4). Another explanation of this effect which was suggested by the results of the experiments reported in Chapters 3 and 4 will be considered in this chapter. It was postulated that the septum is part of an inhibitory or satiety system for the control of water intake.

In Chapter 3, it was reported that rats with septal lesions do not drink more frequently but, when drinking does occur, each bout is longer. This suggested that there might be some deficit in the mechanisms responsible for the cessation of drinking. Another indication that the septum might be involved in the termination of water intake came from Chapter 4. Rats with septal lesions increased water intake when it was readily available, but

were no longer hyperdipsic when they had to work by pressing a number of times for each water reward. This result, similar to the effects of ventro-medial hypothalamic lesions on food intake, could be due to the disruption of an inhibitory or satiety system for water intake. The experiment reported in this chapter was undertaken as a more direct test of this hypothesis. Electrical stimulation was administered to the septum during ad libitum drinking, or during drinking for one hour following 23 hours of water deprivation. A reduction in water intake produced by septal stimulation would support the hypothesis that the septum is part of an inhibitory system for water intake.

METHOD

Subjects (Ss): The Ss were 10 male, black-hooded rats, 3 mon. of age and weighing 225 to 250 gm. at the time of surgery.

Apparatus: Each S was housed individually in a metal cage similar to that described in Chapter 2. During each test, the cage was placed in a wooden stand, 31 cm. long by 28 cm. wide by 36 cm. high. A mercury commutator was suspended over the top of the cage. Electrical stimulation was delivered from a Grass S4 stimulator and, in part 1 of the experiment, the stimulation was controlled by a Hunter Recycling Timer (Model 124S). In part 2, a movement detector

(Electrocraft of Canada Ltd.), which was placed under the water spout, acted as a transducer and permitted recordings to be made of the lap rate on a Grass polygraph (Model 7).

Procedure: Each S was anaesthetized with sodium pentobarbital (40 mg./kgm.) and placed in a stereotaxic apparatus. With the head level, a bipolar nichrome electrode (0.025 in. diameter, Plastic Products Ltd., Roanoke) was stereotaxically implanted into the septal region of each rat brain. The electrode was held in place permanently by means of jeweler's screws and dental cement. An intramuscular injection of penicillin was given following the operation, and each S was allowed at least 1 wk. of recovery.

At the end of testing, the Ss were sacrificed, and the histological procedure described in Chapter 2 was carried out to permit localization of the electrode tip.

One wk. after surgery, all Ss were extensively pretested in an open field situation to determine the voltage required to produce either motor movements or behavioural arrest. In the subsequent tests, the voltage applied to each S was lowered to less than 1/2 that that required to produce one or both of these responses.

Intermittent, biphasic, square-wave, brain stimulation of 0.10 msec. pulse duration was delivered to

the septal region at a frequency of 50 pulses/sec. The stimulation was programmed by means of the Hunter Recycling Timer to occur once every 70 sec., for a duration of 10 sec.

In the first part of the experiment, the S was allowed food and water ad libitum, and the electrical stimulation was presented for a period of 24 hr., after which, water intake, food intake, and urine output were measured and compared to control values. Each S was tested 3 times with a 10 day interval between tests. Subsequently, electrical brain stimulation was delivered during 1 hr. sessions with water and food available following 23 hr. of water deprivation. Again, water intake, food intake, and urine output were measured and compared to control values. This procedure was repeated twice for each S with a 10 day interval between sessions.

In the second part of the experiment, electrical stimulation of the septal region was made contingent upon lapping at a water spout, such that each contact with the spout closed the drinkometer relay, which activated the Grass S4 stimulator. The frequency of stimulation was 50 pulses/sec., and the pulse duration was 0.10 msec. The intensity of stimulation was varied from 0 to 5 volts in a random fashion for each S. Testing sessions were of 10 min. duration. The rate of lapping was recorded for each S by means of the movement detector and pen oscillograph,

and the volume of water consumed during the session was recorded.

The Ss were subsequently tested to determine the effects of the electrical stimulation on food intake. The Ss were food deprived for 23 hr., and then retested as in part 1 of the experiment.

RESULTS

Fig. 8 is an example of an electrode placement in the septum. As shown in Fig. 9, all of the electrodes were located in the antero-medial region, 7 in the lateral septum, and 3 in the medial region. Similar results were obtained from all of the electrode placements.

The effects of intermittent septal stimulation over a 24 hr. period are presented in Table 8. During the control sessions, the average water intake was 38.0 ml., while during the stimulation period, water intake fell to 28.1 ml., a highly significant difference ($t=5.5$, $df=9$, $p<.01$). This effect was observed in each of the animals. In contrast, there appeared to be no effect of the stimulation on urine output ($t=.54$, $df=9$, $p>.10$); the animals excreted as much during the experimental period as during the control period. The stimulation had a slight, but nonsignificant, effect on food intake ($t=1.2$, $df=9$, $p>.10$). During control sessions, the average intake was 23.2 gm., compared to 21.6 gm. during the experimental sessions.

Fig. 8. Photomicrograph of a section through the septal region of No. 63, showing the electrode placement.

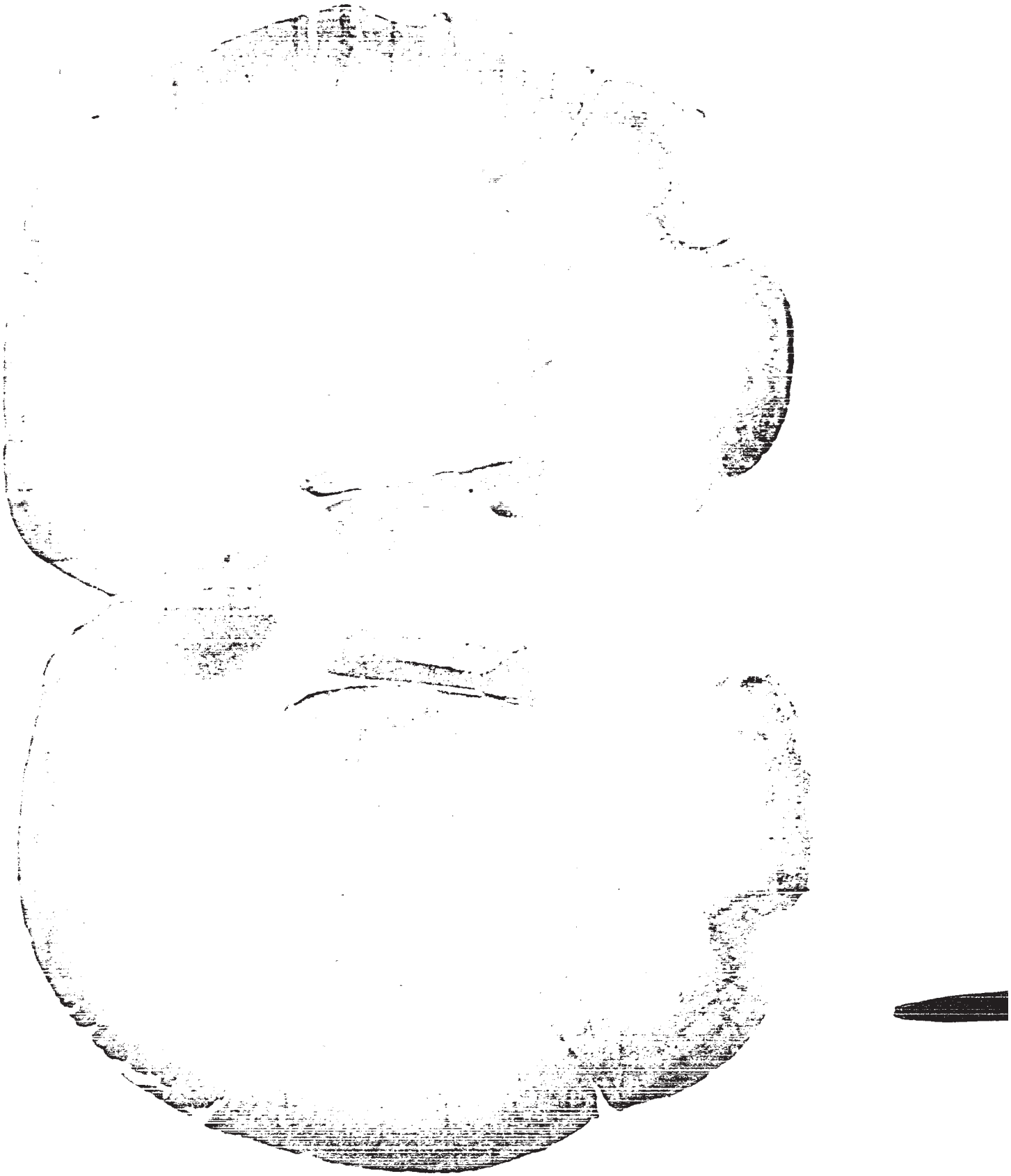


Fig. 9. Drawing of serial sections through the septal region of the rat brain showing the location of all electrode placements in experiment 4.

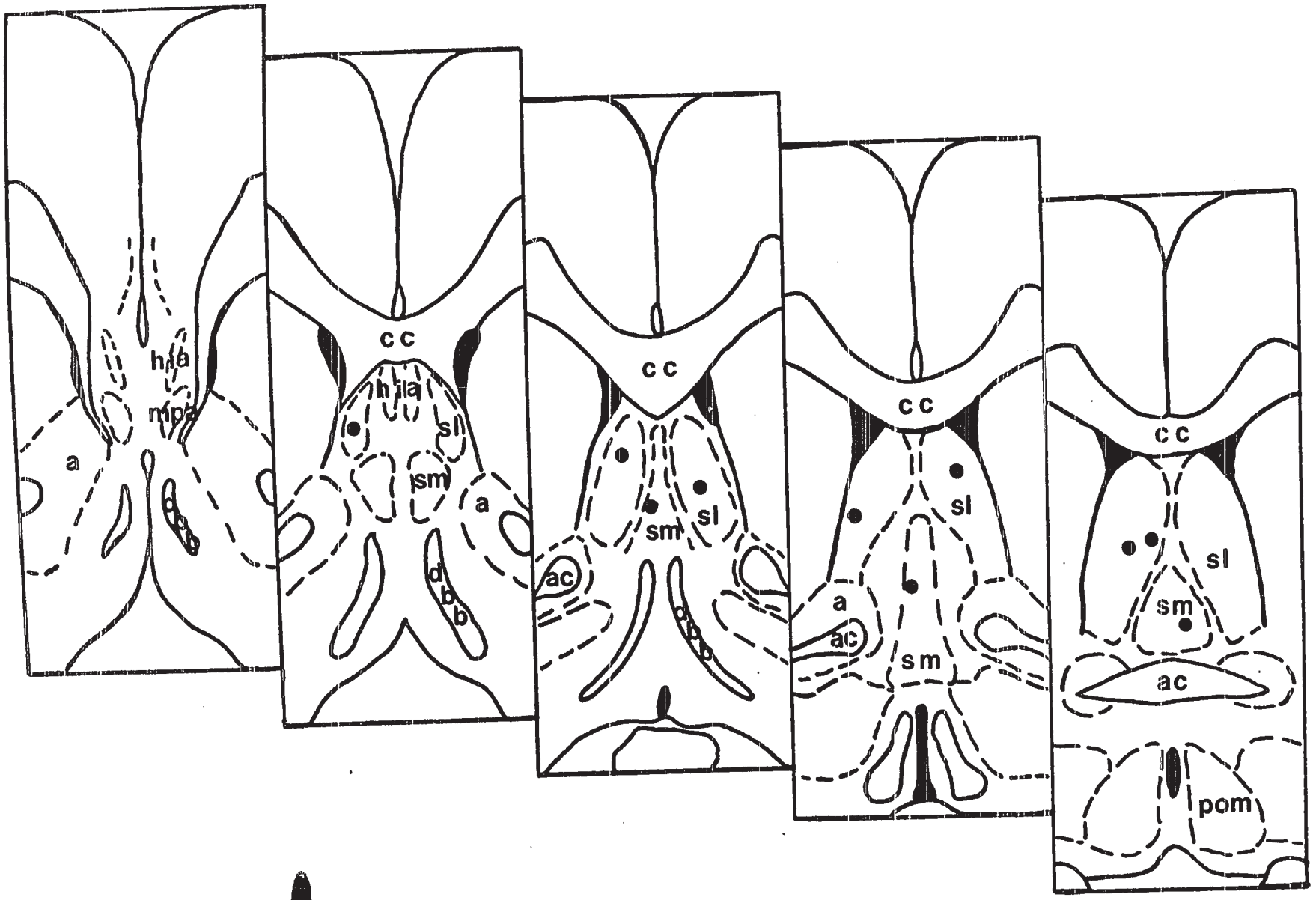

cc
hla
mpa
a
sl
sm
ac
pom

TABLE 8

Effects of 24 Hour Septal Stimulation on Water Intake, Food Intake and Urine Output

	Control	Stimulation
Water Intake (ml.)	38.0 ± 2.6	28.1 ± 2.1*
Food Intake (gm.)	23.2 ± 1.8	21.6 ± 2.0
Urine Output (ml.)	14.8 ± 1.9	14.1 ± 1.2

Values are means ± standard deviations.

* Significant at .05 level

In Table 9, it can be seen that electrical stimulation of the septum for 1 hr., following 23 hr. of water deprivation, significantly depressed water intake ($t=3.1$, $df=9$, $p<.02$). The effect was again observed in each of the 10 rats. The volume of urine was so small that no valid comparisons could be made. None of the Ss consumed any food during the 1 hr. in which water was available. In addition, septal stimulation applied during the 1 hr. in which food was available following 23 hr. of food deprivation had no reliable effect on food intake ($t=.89$, $df=9$, $p>.30$).

Water intake as a function of the voltage of stimulation during 10 min. drinking sessions is plotted in Fig. 10. Each contact with the spout caused a pulse train of electrical stimulation to be delivered to the septal region. As the voltage increased beyond 1.5 V., water intake decreased in a near linear fashion. Beyond 5 V., overt head movements and violent shaking were sometimes elicited by the stimulation.

The effects of septal stimulation on the drinking pattern are illustrated in Fig. 11. In the upper part of the figure (A), no stimulation was applied and the rat engaged in long bouts of drinking, stopping occasionally to swallow and to make postural adjustments. In the bottom

TABLE 9

Effects of 1 Hour Septal Stimulation Following 23 Hours of Water or Food Deprivation

	Water Deprivation	
	Control	Stimulation
Water Intake (ml.)	18.1 ± 1.4	15.9 ± 1.7*
Food Intake (gm.)	0	0
Urine Output (ml.)	1.1 ± 0.5	0.9 ± 0.6
	Food Deprivation	
	Control	Stimulation
Food Intake (gm.)	13.7 ± 2.4	14.1 ± 2.2

* Difference significant at .05 level.

Values are means ± standard deviations.

Fig. 10. Mean water intake during 10 minute tests as a function of current intensity delivered to the septum following 23 hours of water deprivation.

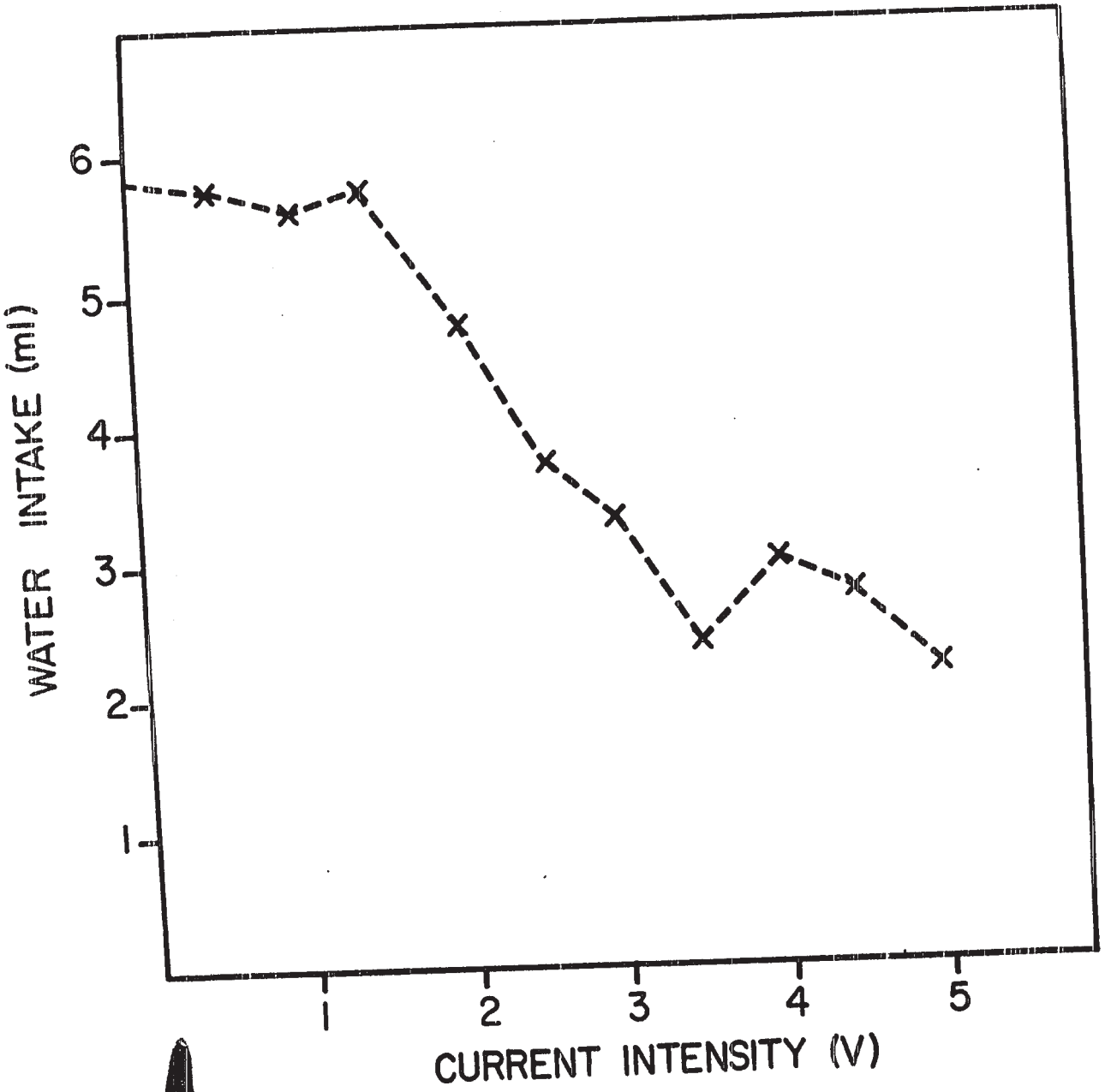
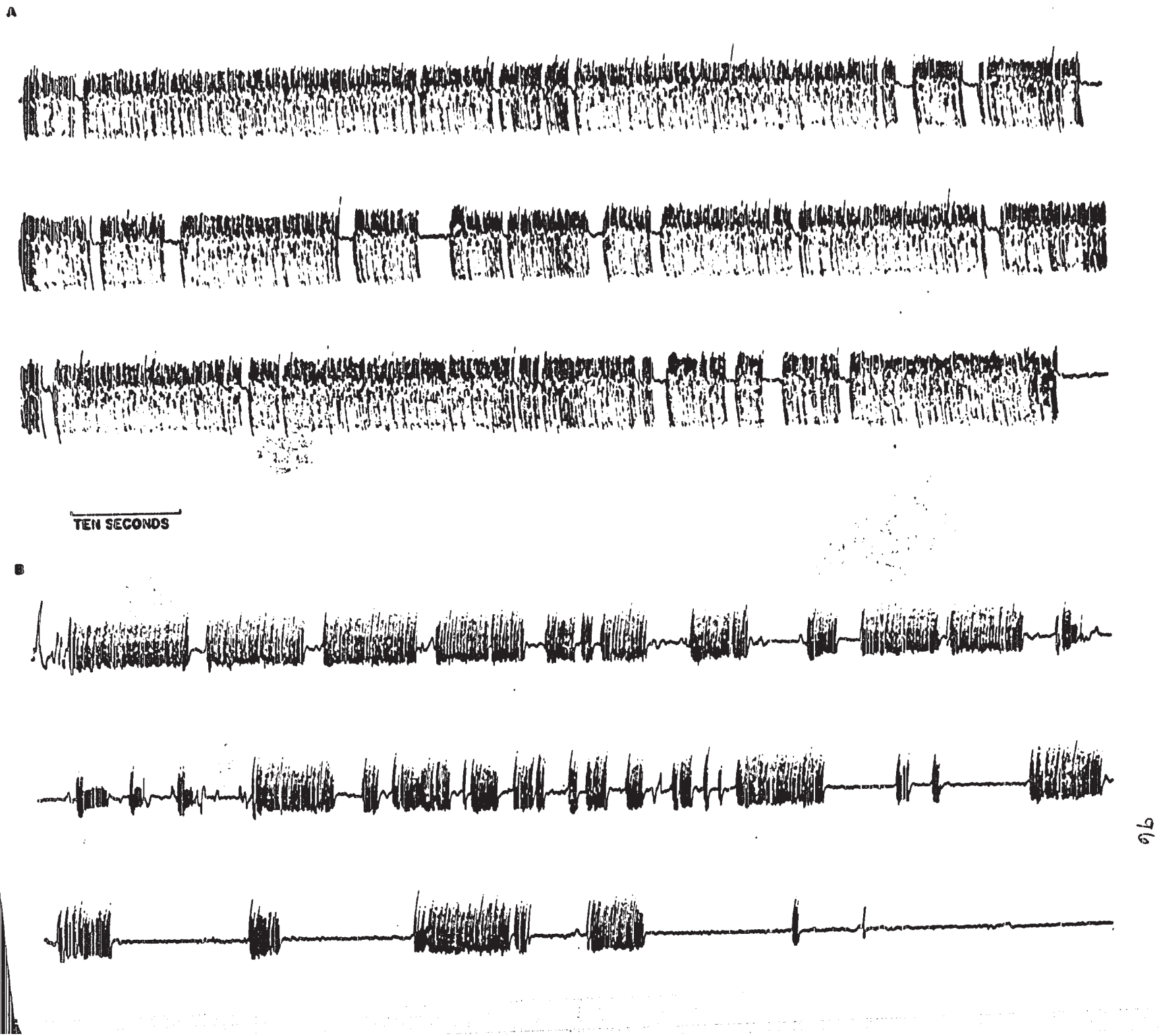

WATER INTAKE (ml)
6
5
4
3
2
1
1
2
3
4
5
CURRENT INTENSITY (V)

Fig. 11. Effects of septal stimulation on the drinking pattern of the rat. A--control. In B, septal stimulation delivered with each lap.


A
TEN SECONDS
B

record (B), each lap caused a brief pulse train to be delivered to the septum and clearly, this stimulation increased the number and length of pauses until, finally, the rat stopped drinking altogether. Fig. 12 demonstrates that septal stimulation had no effect on the lap rate. In both the top (A-no stimulation) and bottom (B-stimulation) records, the lap rate was approximately 7/sec. Again, however, the interval between bouts of lapping was longer in the stimulation record.

DISCUSSION

The results of this experiment demonstrate that water intake in both ad libitum and water deprived rats, is reduced by electrical stimulation of the septum. They confirm and extend the observations of Mabry and Peeler (1968) who reported that septal stimulation applied during a 30 minute session reduced water intake. In particular, the present results make it possible to rule out certain interpretations of the effects of septal stimulation on water intake and support the suggestion that the septum plays a role in the termination of drinking.

Since electrical stimulation of the septum has been reported to have a general inhibitory effect on autonomic and somatic behaviours (Covian et al., 1964; Kaada, 1951), it is necessary to consider the possibility that

Fig. 12. Effects of septal stimulation on the lap rate of the rat. A--control. In B, septal stimulation delivered with each lap.

FIVE SECONDS

septal stimulation has a similar inhibitory effect on various consummatory behaviours. This does not seem to be the case. Although water intake was significantly reduced by septal stimulation, food intake was not affected appreciably. The slight reduction in food intake during the 24 hour testing session is probably secondary to the reduced water intake. Normally, food and water intakes are closely related, and a rat that consumes less water also eats less (Cizek, 1961; Kissileff, 1969).

Lesions of the septum cause response perseveration (McCleary, 1961), and, as reported earlier, septal stimulation inhibits both reflexive and cortically induced movements (Kaada, 1951). It may be suggested, therefore, that the septal stimulation of the present study was merely influencing the motor components concerned with drinking, and thereby reducing water intake. Although with higher voltages behavioural or motor arrest was observed, such effects did not occur with the lower intensities of stimulation employed in the experiment. The lap rate, which should be vulnerable to such arrest effects, was not reduced by septal stimulation. It has been reported that stimulation of the septal region can reduce the lap rate (from 6 to 8 /second to 2 to 3/second), but this is presumably with a higher current intensity that does induce

motor arrest (Asdourian, 1962). Rather than affecting lap rate, the results of the present experiment show that the septal stimulation caused the animal to terminate drinking sooner (after a smaller number of laps). The interpretation offered for this observation is that stimulation of the septum activates an inhibitory system for the control of water intake.

Another possibility that cannot be ruled out conclusively is that septal stimulation is aversive and that consummatory behaviour was negatively reinforced. Such an effect could have occurred when the stimulation was contingent upon lapping the water spout. It is unlikely to have occurred, however, when the stimulation was applied by a programmer. Also, if drinking was negatively reinforced by the stimulation, feeding should have been as well. Since food intake was not reduced by the stimulation, this does not seem to have occurred. Furthermore, all of the rats were good self-stimulators, and it is unlikely that the stimulation was positively reinforcing in one situation, and aversive or negatively reinforcing in another.

The results of experiments in which the septum has been chemically stimulated suggest that the septal region facilitates water intake (Fisher and Coury, 1962; Grossman, 1964). It is possible that septal stimulation facilitates

water intake, but that this facilitation is overcome by a long lasting, post-stimulation inhibition. However, when septal stimulation was contingent upon lapping, the bouts of drinking were shorter than when no stimulation was applied. This is in direct contradiction to the above hypothesis which would predict longer bouts of drinking under these conditions.

The final interpretation of the results to be presented is that electrical stimulation of the septal region reduces water intake by activating an inhibitory system which influences the drinking system of the lateral hypothalamus. This inhibitory effect on the lateral hypothalamus could be direct, or it might be mediated by the ventromedial hypothalamus, or some other region of the limbic system or pathway to the hypothalamus. As mentioned above, the stimulation applied to the septal region did not cause an abrupt termination of drinking. The animal continued lapping at the water spout although the bouts of lapping were shorter than when no stimulation was applied. With increasing intensity of stimulation, the bouts of lapping became shorter and shorter. These observations suggest a gradual build-up of inhibition, leading to the cessation of drinking.

Additional evidence suggesting that the septum

has inhibitory effects on the lateral hypothalamus has come from self-stimulation experiments. Lorens (1966) has reported that lesions of the septum enhance the rate of self-stimulation of the lateral hypothalamus, and Keesey and Powley (1968) have shown that such lesions reduce the threshold for lateral hypothalamic self-stimulation. Unfortunately, there is no empirical evidence that lesions of the septum affect drinking induced by stimulation of the lateral hypothalamus, although this would have important implications for the hypothesis outlined in the preceding paragraph.

CHAPTER 6

If, as suggested by the results of the previous experiment, the septum is part of an inhibitory system for water intake, it is apparently influenced by food deprivation. An incidental observation made in the experiment reported in Chapter 3 showed that even rats with septal lesions which did not increase their ad libitum water intake became hyperdipsic during a period of food-deprivation. This finding was the basis for the experiment of Chapter 6. Rats with lesions of the septum were deprived of food for 72 hours, and the effects of the food deprivation on water intake and urine output were observed. In addition, the capacity to concentrate urine during water restriction was studied.

The results of Chapter 3 showed that even in the septal rat, water intake is closely associated with food intake. This behaviour was further investigated in the present chapter. Rats with septal lesions were deprived of

food or water or both food and water, and comparisons were made of the volumes of water consumed in the presence or absence of food.

METHOD

Subjects (Ss): The Ss were 36 male, black-hooded rats, 3 mon. of age and weighing 250 to 300 gm. at the time of surgery.

Procedure: The Ss were housed individually in cages similar to those described in Chapter 2. For 2 wk. prior to surgery, water and food intakes and urine output were measured. The Ss were then divided into 2 groups matched for water intake corrected for body weight. Ss in the first group received sham operations, and the Ss in the second group received septal lesions according to the procedures described in Chapter 2. The post-operative recovery period was 3 wk., during which food and water intakes and urine output were measured and compared to pre-operative values.

All Ss were food deprived for 72 hr. starting immediately after the recovery period. Water intake and urine output were measured at the end of 24, 48, and 72 hr. One wk. later, the Ss were again food deprived for 72 hr., and similar observations made. One wk. later, the Ss were water deprived, and urine outputs measured at the end of 24 hr.

To determine the relationship between feeding and drinking of the septal animals, the procedure outlined in

Table 10 was followed. Various combinations of food, water, or food and water deprivation of 24 hr. duration were given. Following the deprivation period, the Ss were allowed access to food or water or both, for 24 hr., and measurements were made of the water intake by each S.

RESULTS

The group data for all 36 rats appear in Table 11. As in Chapter 2, it was found that following surgery, not all Ss with lesions of the septal area increased their daily water intake. Only 11 of the 18 Ss in the experimental group showed elevated water intakes post-operatively. The remaining 7 Ss were indistinguishable from the controls. The septal drinkers consumed significantly more water than the controls or septal nondrinkers when water and food were available ad lib. ($F=7.46$, $df=2,30$, $p<.01$). The increase in water intake ranged from 12.0 to 85.1 ml. water/day.

As in Experiment 1, the food consumption of the septal drinkers was depressed immediately after surgery (Table 12), but the difference was not statistically significant ($F=1.61$, $df=2,30$, $p>.10$). There were no differences in food intake between the groups during any phases of the experiment when food and water were available. Both septal drinkers and nondrinkers lost a significant amount of weight immediately after surgery, but thereafter gained weight at the same rate as the operated controls (Fig. 13).

TABLE 10

Pre-Treatment and Testing Schedule for the Measurement of the Relationship between Food and Water Intake

		Pre-Treatment Condition (24 hr.)	Testing Condition (24 hr.)
A.	1.	Water and Food Deprivation	Access to food and water
	2.	Water and Food Deprivation	Access to water only
B.	1.	Water Deprivation	Access to food and water
	2.	Water Deprivation	Access to water only
C.	1.	Food Deprivation	Access to food and water
	2.	Food Deprivation	Access to water only

TABLE 11

Pre- and Post-Operative Water Intakes of Controls, Septal Nondrinkers and Drinkers

	N	Water Intake (ml.) Pre-Operative	Post-Operative
Con	18	34.2 ± 2.2	35.1 ± 2.8
SN	7	35.3 ± 2.7	39.4 ± 3.1
SD	11	35.0 ± 2.5	51.6 ± 5.1

Values reported are means ± standard deviations.

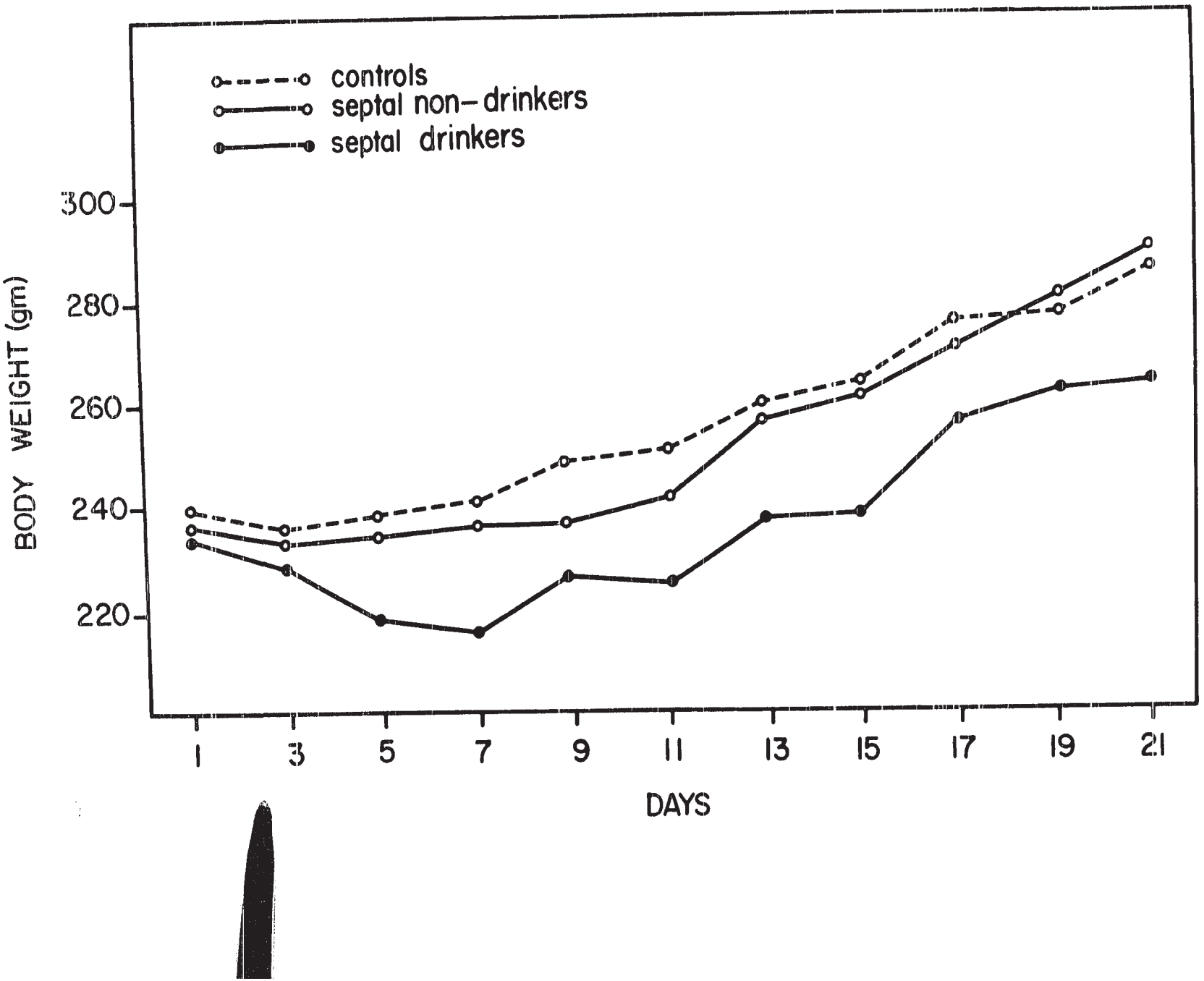
TABLE 12

Food Intakes of Controls, Septal Drinkers and Nondrinkers

	Food Intake (gm.)				
	Pre-Op.	Wk. 1	Wk. 2	Wk. 3	Wk. 4
Con	23.0 ± 1.4	22.4 ± 1.6	23.6 ± 1.7	24.1 ± 1.9	23.8 ± 1.7
SN	23.3 ± 1.5	21.8 ± 1.0	22.4 ± 1.4	22.8 ± 1.9	22.6 ± 1.6
SD	22.6 ± 1.7	20.4 ± 2.0	24.1 ± 2.2	24.4 ± 1.7	25.2 ± 2.3

Values reported are means ± standard deviations.

Fig. 13. Mean body weights of controls, septal nondrinkers and septal drinkers following surgery.


controls
septal non-drinkers
septal drinkers
BODY WEIGHT (gm)
300
280
260
240
220
1
3
5
7
9
11
13
15
17
19
21
DAYS

The results obtained when the animals were placed on 72 hr. of food deprivation are shown in Fig. 14. After 24 hr. of food deprivation, the operated control rats decreased both their water intake and urine output. With longer periods of food deprivation, these effects were enhanced. The septal drinkers did not reduce their water intake below pre-deprivation values during the initial (24 hr.) food deprivation period. With longer periods of food restriction, both water intake and urine output decreased, but the volumes always exceeded those of the operated controls ($t=2.49$, $df=27$, $p<.05$).

Whereas the septal drinkers showed a relative hyperdipsia during food deprivation, the septal nondrinkers actually showed an absolute increase of water intake during the 24 hr. food deprivation period. This was matched by an increased urine output. For all of the periods of food restriction, this group did not differ from the septal drinkers for water intake or urine output ($t=1.52$, $df=16$, $p>.10$), although prior to deprivation, both water intake and urine output were significantly less.

The average volumes of urine excreted by the Ss of the 3 groups during 24 hr. of water deprivation are shown in Table 13. There were no significant differences among the groups ($F=0.93$, $df=2,30$, $p>.10$). Clearly, both septal drinkers and nondrinkers were capable of reducing

Fig. 14. Mean water intakes and urine outputs of controls (open bars), septal nondrinkers (dotted bars), and septal drinkers (cross-hatched bars) under ad libitum conditions and following various periods of food deprivation.

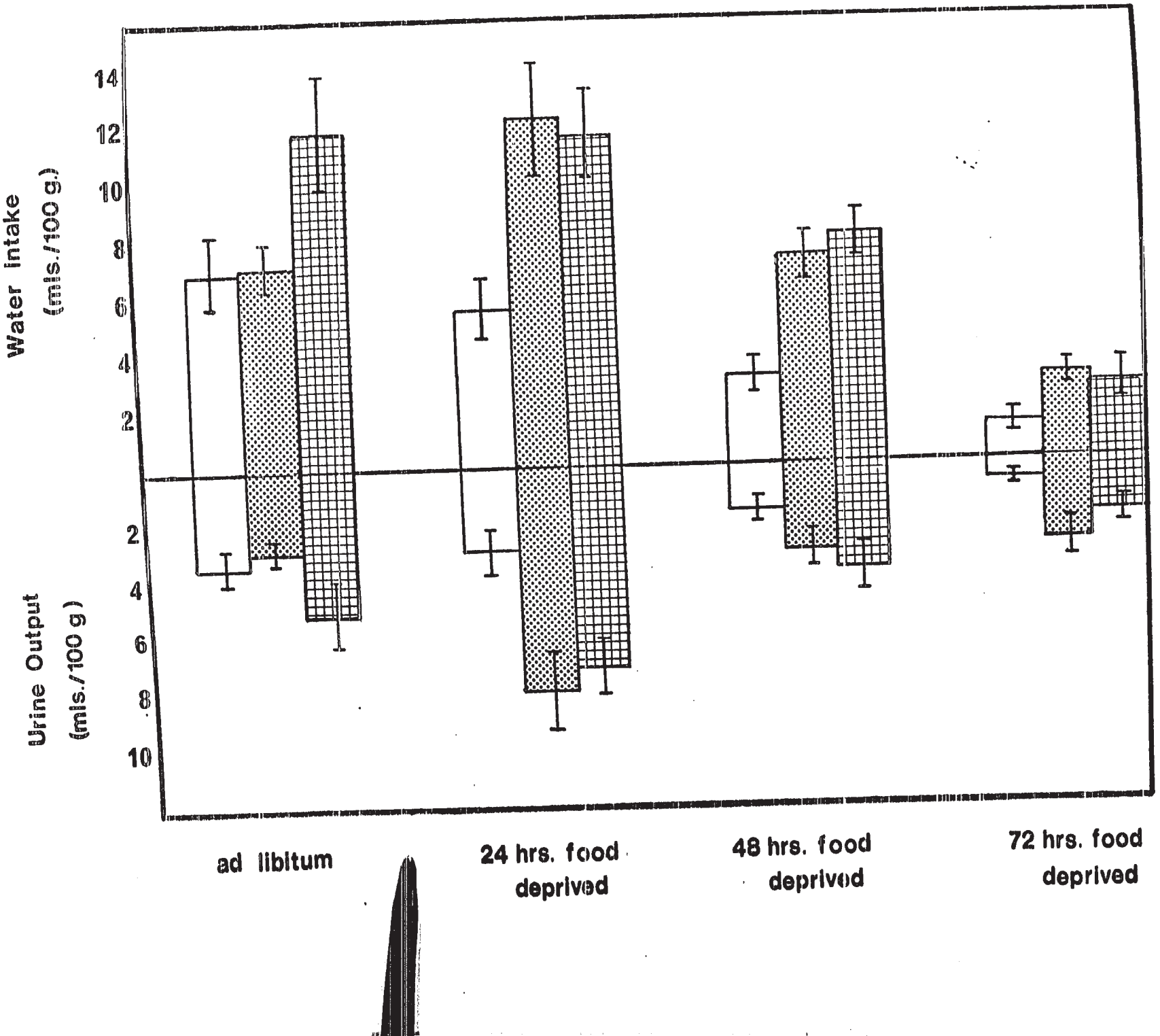

Water Intake
(mls./100 g.)
14
12
10
8
6
4
2
Urine Output
(mls./100 g.)
2
4
6
8
10
ad libitum
24 hrs. food deprived
48 hrs. food deprived
72 hrs. food deprived

TABLE 13

Urine Output During 24 Hours of Water Deprivation of Controls, Septal Nondrinkers and Drinkers

	N	Urine Output*
Con	18	1.1 ± 0.6
SN	7	0.9 ± 0.8
SD	11	1.0 ± 0.8

* Values are means (ml./100 gm. body weight), ± standard deviation.

urine output at least as well as controls.

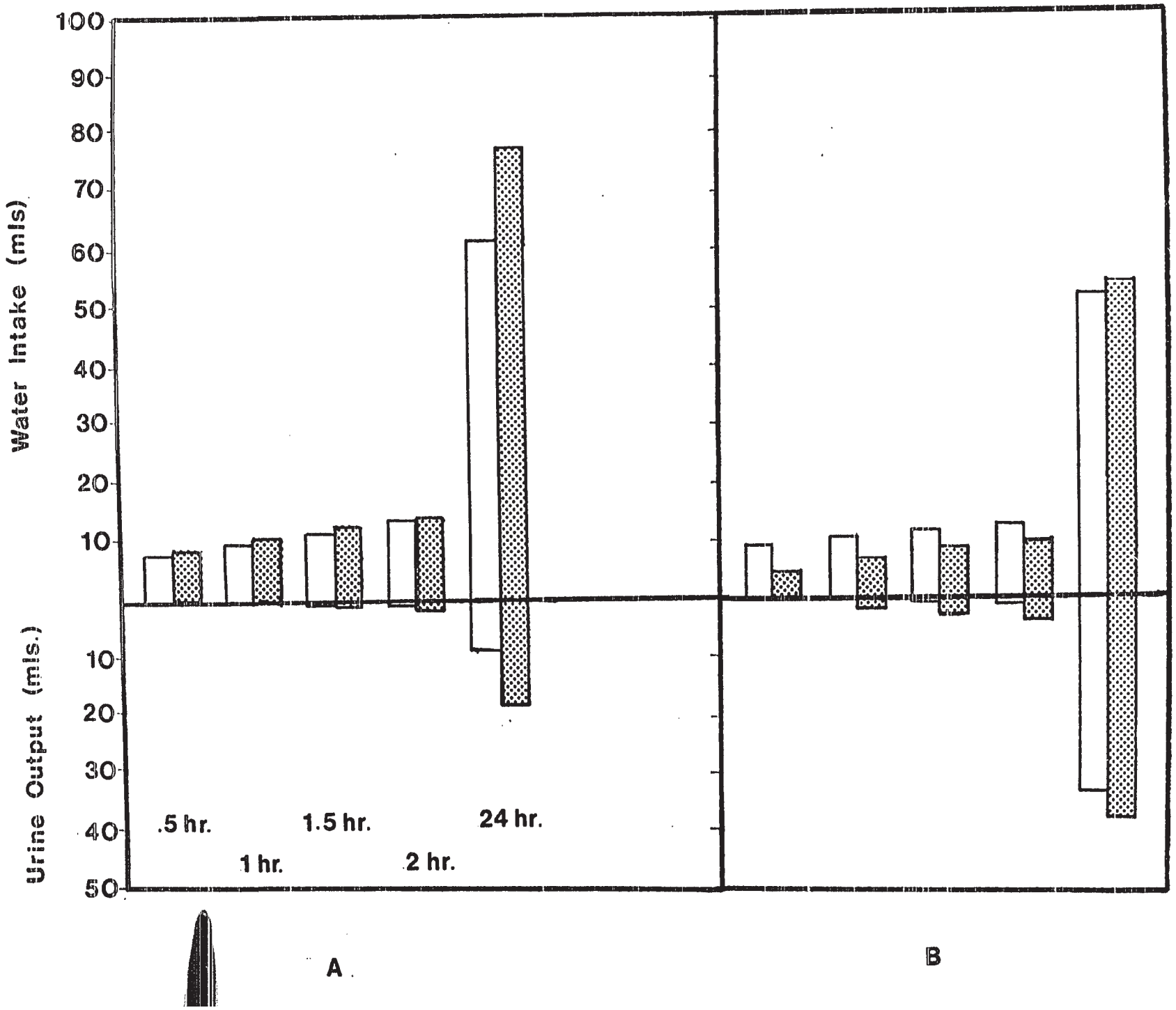
The result of the second part of the experiment are presented in Figs. 15 to 17. In Fig. 15a, it is evident that following the reintroduction of food and water after a period of food and water deprivation, the septal drinkers consumed more water than the controls ($t=4.51$, $df=27$, $p<.05$). However, when only water was reintroduced (Fig. 15b), there was no difference in water intake between the 2 groups ($t=1.01$, $df=27$, $p>.10$). As shown in Fig. 16, the septal drinkers drank more water than the controls following a period of water deprivation whether food was present or not ($t=3.77$, $df=27$, $p<.05$). Finally, as shown in Fig. 17, when the animals were food deprived for 24 hr. and then permitted access to water, the septal drinkers drank more water than the controls with food either present or absent ($t=3.3$, $df=27$, $p<.05$).

Thus, following a period of either food or water deprivation, rats with septal lesions drank more water than controls. Also, even when food and water deprived and then permitted access to food and water, the septal animals drank more water than controls.

DISCUSSION

Water intake and urine output during 24 hours of food deprivation were well below ad libitum values in the control rats, confirming previous observations (Lepkovsky

Fig. 15. Mean water intakes and urine outputs of controls (open bars) and septal drinkers (dotted bars) following food and water deprivation. A--food and water present. B--water only present.


Water Intake (mls)
Urine Output (mls.)
100
90
80
70
60
50
40
30
20
10
10
20
30
40
50
.5 hr.
1 hr.
1.5 hr.
2 hr.
24 hr.
A
B

811

Fig. 16. Mean water intakes and urine outputs of controls (open bars) and septal drinkers (dotted bars) following water deprivation. A--food and water present. B--water only present.

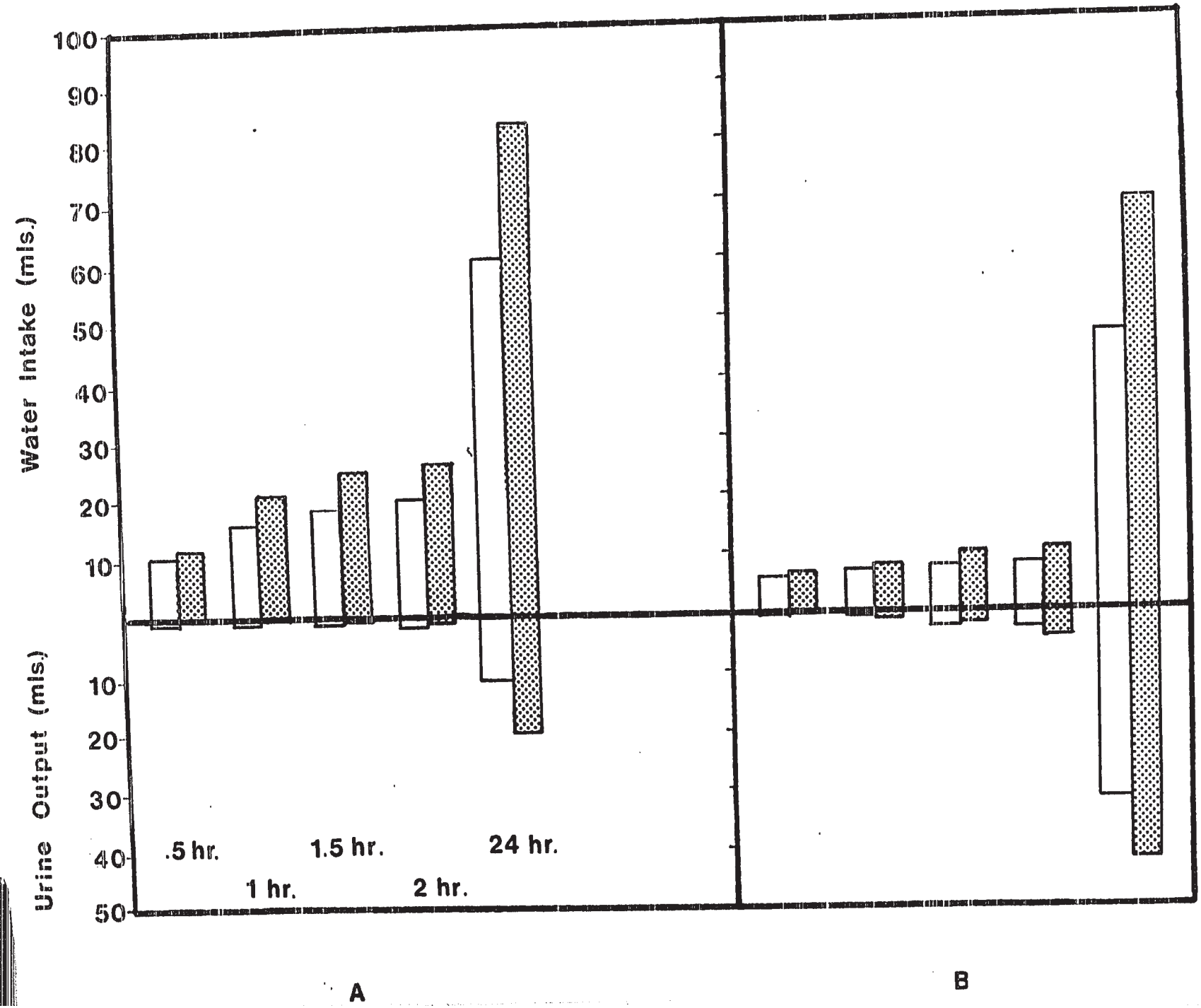
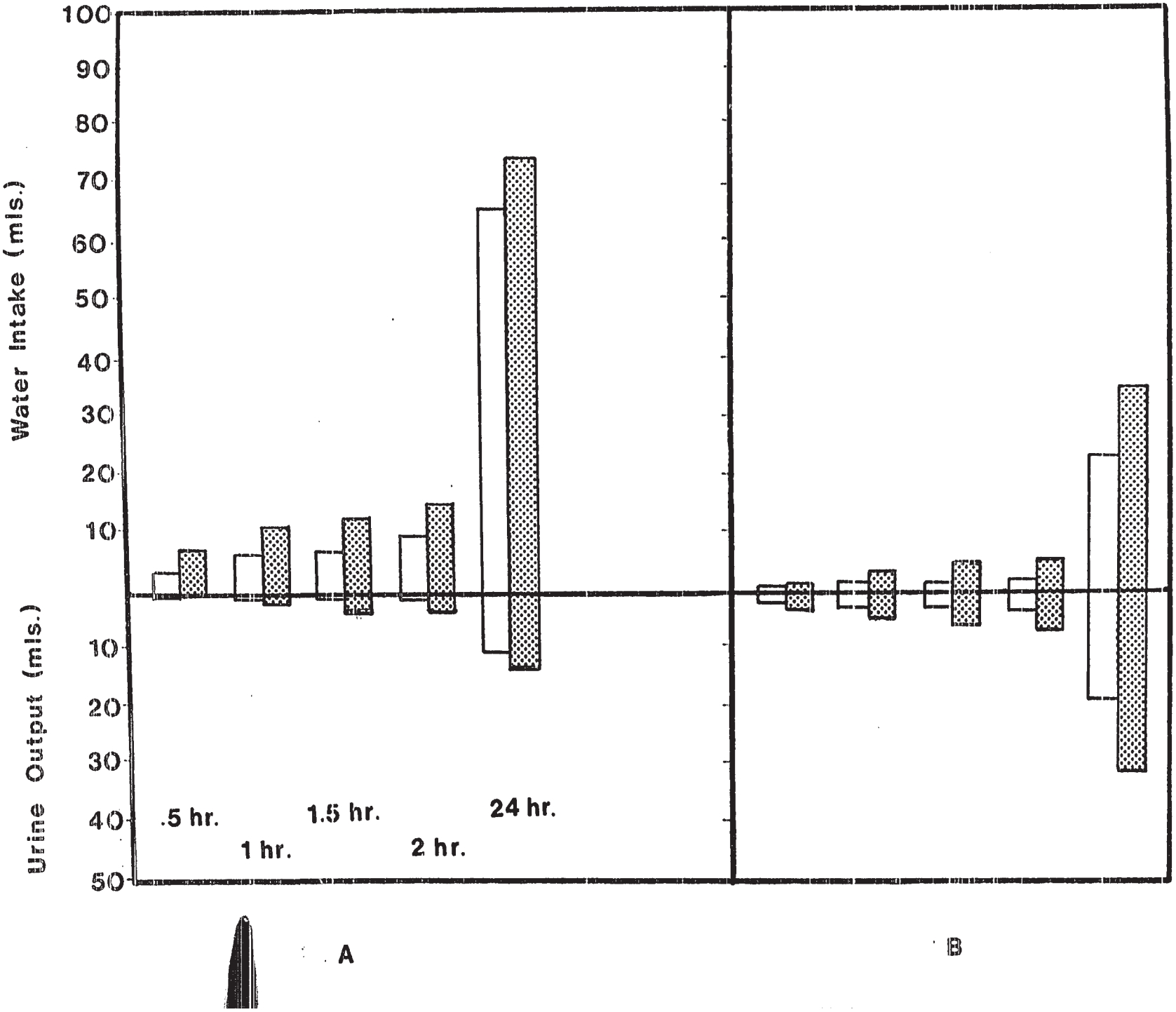

Water Intake (mls.)
Urine Output (mls.)
100
90
80
70
60
50
40
30
20
10
10
20
30
40
50
.5 hr.
1 hr.
1.5 hr.
2 hr.
24 hr.
A
B

Fig. 17. Mean water intakes and urine outputs of controls (open bars) and septal drinkers (dotted bars) following food deprivation. A--both food and water present. B--water only present.


Water Intake (mls.)
Urine Output (mls.)
100
90
80
70
60
50
40
30
20
10
10
20
30
40
50
.5 hr.
1 hr.
1.5 hr.
2 hr.
24 hr.
A
B

et al., 1967; Morrison, 1968). Lepkovsky and his associates suggested that since water requirements become less in starvation, water intake and urine output are reduced. Rats with lesions of the septal area, however, maintained a high level of water intake and also increased urine output during the 24 hour food deprivation period. Since it was observed that these Ss were capable of reducing urine output during water deprivation, the increase in urine output during food restriction seems to be secondary to the high level of water intake. Although not as much water is needed to maintain water balance (i.e., the solute load becomes less and less as starvation progresses), water intake remains elevated; a marked diuresis ensues.

The reason septal animals (both drinkers and non-drinkers) show hyperdipsia during food restriction is not clear. Coury (1967) has suggested that the septal area may be involved in 'matching' water intake to food intake, since the local application of carbachol or noradrenalin to the septum produces drinking and feeding respectively. According to Coury, water intake is 'bound' to food intake in the normal rat such that the volume of water intake each day is in direct proportion to the quantity of food consumed. This relationship between food and water intakes explains the well-known observation that intact rats reduce their water intake during food deprivation, and the fact

that rats undergoing water deprivation reduce their food intake (Adolph, 1947; Cizek, 1961). Lesions in the septal area might remove the 'coupling' between food and water intake, making each, to some degree, independent of the other. This uncoupling could be the reason why septal animals do not reduce their water intake when food deprived. However, two observations do not support this hypothesis. First, a slight elevation in food intake of the septal drinkers was observed in Experiment 1. It would thus appear that, in the septal rat, elevated water intake is accompanied by increased food intake. Also, in the second part of the present experiment, the septal drinkers (as well as the controls) always drank more water when food was present than when it was not. Moreover, under ad libitum conditions, drinking in the septal rat usually occurs with feeding (Chapter 3; Blass and Hanson, 1970). Thus, the relationship or 'coupling' between water intake and food intake does not appear to be disturbed by septal damage.

Morrison (1968) has shown that normal rats undergoing food deprivation maintain themselves in a state of 'relative hyperdipsia' (drink less than usual, but in excess of apparent requirements) during the initial stages of starvation. Furthermore, food deprived rats worked for the excess water when the work rate was relatively low, suggesting that they were motivated to consume more water

than they actually needed. Oatley and Tonge (1969) have also observed excessive non-homeostatic drinking by hungry rats injected with saline, and these observations have led them to suggest that hunger may actually cause an animal to drink in excess of apparent need. Since rats with septal damage often show startle and affective responses which are gross exaggerations of normal behaviour, it may be that septal rats remain hyperdipsic during food deprivation due to an exaggeration of a normal response, that of 'relative' hyperdipsia during starvation.

An important factor in the control of water intake is the state of energy balance, and especially food intake. This factor may be more important in understanding the role of the septum in water balance than the primary signals for water intake. As suggested in Chapter 3, there are presumably inhibitory influences on water intake since drinking usually terminates before the water deficit has been satisfied. The results of the present experiment suggest that this inhibitory or satiety influence on water intake fluctuates with the degree of energy deficit (hunger). The normal animal becomes satiated for water much sooner when food-deprived. In the septal animals, especially the septal nondrinkers, the inhibitory effects of water intake are much reduced during food restriction. Although there are probably separate inhibitory or satiety systems for food intake and for water intake, there may be common

inhibitory aspects as well.

In two out of three tests conducted in the second part of the experiment, the septal animals drank more water than controls regardless of the presence or absence of food. These observations support the suggestion of Harvey and Hunt (1965) that septal hyperdipsia is not due to increased food consumption. However, the Ss of both groups always drank more water when permitted to eat at the same time. Thus, as indicated in Chapter 3, the pattern of feeding and drinking is not disrupted by septal damage.

Although the septal animal is affected by the presence or absence of food, there does not appear to be any exaggeration of prandial drinking following the lesion. This finding supports the results of Blass and Hanson (1970). They recorded the temporal relationship between feeding and drinking following the delivery of dry food pellets. They found that rats with septal lesions drink no more often than controls in response to prandial (dry mouth) cues. Rather, longer bouts of drinking occurred. Blass and Hanson (1970) concluded that septal hyperdipsia could not be due to oropharyngeal dryness which would increase the incidence of prandial drinking.

CHAPTER 7

While the experiments reported in this thesis, and the studies made by other investigators establish that large, bilateral lesions of the septum of the rat substantially increase daily water intake, very little is known about the area or areas within the septum responsible for this effect. The results of four studies suggest that the anterior septal region is the critical area for producing hyperdipsia (Harvey and Hunt, 1965; Donovick and Burright, 1967, 1968; Carey, 1967). The results of other experiments indicate that lesions of the posterior septum may affect post-operative water intake (Lubar et al., 1968, 1969; Lorens and Kondo, 1968; Carey, 1969). Finally, Besch and Van Dyne (1969) were unable to localize any region within the septum which must be removed to produce increased water intake. Rather, their results suggest that cell damage or degeneration in the paraventricular nuclei, which may be a consequence of lesions of the septum and which leads to reduced secretion of ADH, is responsible for

the septal hyperdipsia.

This experiment was conducted in order to determine the anatomical locus within the septum which, when removed would produce increased water intake. Electrolytic lesions were stereotaxically aimed at different antero-posterior, dorso-ventral, and medial-lateral placements in the septum, and the histologically verified lesions were correlated with the changes in water intake.

METHOD

Subjects (Ss): The Ss were 36 male, black-hooded rats, 3 mon. of age and weighing 275 to 325 gm., and 25 guinea pigs, approximately 8 mon. of age and weighing 700 to 1,000 gm.

Procedure: Upon being received in the laboratory, each S was weighed and placed in a cage similar to those described in Chapter 2. Water intake was measured daily for the rats by reading the level of water in a graduated tube fastened to the front of the cage, and for the guinea pigs by weighing the water bottles. Body weights were recorded twice weekly. At a specified time each day, all readings were made and the water bottles and food cups refilled.

After 2 wk., the Ss were divided into 2 groups on the basis of water intake corrected for body weight, the groups being as closely matched as possible. The Ss in the control groups received sham operations as described in Chapter 2. Following the operation, each S was given

an intramuscular injection of penicillin and replaced in the home cage.

The animals in the experimental groups were given septal lesions. The electrode was a stainless steel, dental broach (No. 42 Fine, S.S. White Co., Philadelphia), insulated except for 0.5 mm. at the tip. A rectal cathode completed the circuit. The location of the electrode placement was varied from animal to animal in a systematic fashion. Thus, in the rats, in 0.5 mm. steps, lesions were made from anterior 1.5 mm. to anterior 2.5 mm. from bregma, lateral 0.5 mm. to lateral 1.0 mm. from the midline, and ventral 5.5 mm. to ventral 6.5 mm. from the surface of the skull. The incisor bar was set a +2.5 mm. In the guinea pigs, lesions were made from anterior 2.5 mm. to anterior 3.5 mm. from bregma, lateral 0.5 mm. to lateral 1.0 mm., and ventral 6.5 mm. to ventral 7.5 mm. from the surface of the skull. The head was held horizontal. The lesion parameters in all cases were 1.0 mA d.c. for 15 sec. Following the lesion, all Ss were given intramuscular injections of penicillin and replaced individually in cages.

Water intake was recorded daily for 1 mon. after surgery. Body weight was measured twice each wk. during the same period. Thereafter, these measurements were made once weekly for 2 mon., and in several cases, for 3 mon.

Following testing, the experimental animals were

sacrificed and perfused through the heart with saline and 10% formal-saline. The brains were removed and stored in 10% formalin before being frozen sectioned at 20 μ. The sections through and 1 mm. posterior to the lesion were mounted, stained with thionin and examined under the microscope for damage to the various septal nuclei and for evidence of cell damage in the preoptic area.

RESULTS

Four of the 18 rats which sustained damage to the septum died during the post-operative recovery period. The water intake for the controls and for the surviving experimental rats are presented in Table 14. The average daily water intake of the control Ss increased by 0.90 ml./100 gm. of body weight (range -1.1 to +2.2), which was not different from the pre-operative level.

Eight of the 14 experimental Ss became hyperdipsic beginning on the second or third day after surgery, and, as in Chapter 2, were termed septal drinkers. The average amount of water consumed by these Ss increased by 17.0 ml. per day. A sustained weight loss averaging 18 gm. further enhanced the differences in intake between the controls and septal drinkers when adjusted for body weight. Thus, the septal drinkers increased their average daily intake by 5.5 ml/100 gm. body weight (range +2.5 to +16.1).

The remaining 6 rats, which did not show absolute

TABLE 14

Pre- and Post-Operative Water Intake Levels of Rats with Septal Lesions

S	Water Intake*	
	Pre-Operative	Post-Operative
110	35.3 ± 1.7	49.1 ± 2.4
111	37.2 ± 2.0	39.3 ± 2.1
112	36.4 ± 1.9	35.7 ± 1.7
114	33.6 ± 1.5	36.0 ± 1.5
115	39.4 ± 2.2	58.6 ± 2.9
116	37.5 ± 2.0	40.0 ± 1.7
117	30.6 ± 0.9	31.0 ± 1.1
118	41.4 ± 2.4	62.3 ± 3.1
119	39.6 ± 1.6	56.5 ± 2.6
120	44.1 ± 1.8	57.2 ± 2.2
121	42.6 ± 2.0	63.7 ± 2.4
122	38.7 ± 1.3	39.9 ± 1.5
123	35.7 ± 2.1	48.8 ± 2.5
125	33.6 ± 1.4	52.4 ± 2.2

* Values are means (ml./100 gm. body weight), ± standard deviations.

hyperdipsia, were termed septal nondrinkers. Of these, 4 lost weight following surgery and were relatively hyperdipsic.

Table 15 indicates, for each S, the structures which were damaged by the lesion. Most of the lesions produced were quite small (except for those which were located near the ventricles), and tended to involve an elliptical area of tissue surrounding the electrode tip. Reconstructions of the lesion produced in each S are presented in Appendix B.

The area most consistently damaged in the septal drinkers was in the anterior portion of the medial septum. The cross-hatched area of Fig. 18 indicates this general region. Fig. 19 is a photomicrograph of a coronal section through the septum, showing the extent of damage produced in S115. As indicated in Table 15, this S suffered damage only to the medial septum.

In several cases, damage to the septum occurred without including the medial septal area outlined above. Thus, destruction of the superior fornix (Ss 116, 122), nucleus accumbens (Ss 114, 122), precommissural fornix (Ss 114, 122), nucleus septofimbrialis (S116), and nucleus triangularis septi (S122), occurred without increased water intake. Rather, these lesions were associated with a slight weight loss and relative hyperdipsia.

TABLE 15

List of Structures Damaged by Septal Lesions Produced in Subjects 110 to 125

	Structures													
S	sm	dbB	sl	HIA	sf	st	FS	FPC	a	TSHT	CPU	CC	pom	f
110	X	X	X				X					X		
111			X	X			X					X		
112			X	X			X							
114			X				X	X	X	X				
115	X	X												
116			X		X		X							
117			X				X					X		
118	X	X							X				X	X
119	X		X	X			X							
120	X		X							X	X	X		
121			X	X			X		X	X				
122						X	X	X	X					X
123	X	X	X	X				X						
125	X	X	X			X								X

List of abbreviations: ms, medial septal nucleus; dbB, diagonal band of Broca; sl, lateral septal nucleus; HIA, Hippocampus, pars anterior; sf,nucleus septalis fimbrialis; st, nucleus septalis triangularis; FS, superior fornix; FPC, pre-commissural fornix; a, nucleus accumbens septi; TSHT, septo-hypothalamic tract; CPU, caudate-putamen; cc, corpus callosum; pom, nucleus preopticus medialis; F, fornix.

Fig. 18. Drawing of serial sections through the septal region of the rat brain, showing the general area consistently damaged in the septal drinkers of experiment 6.

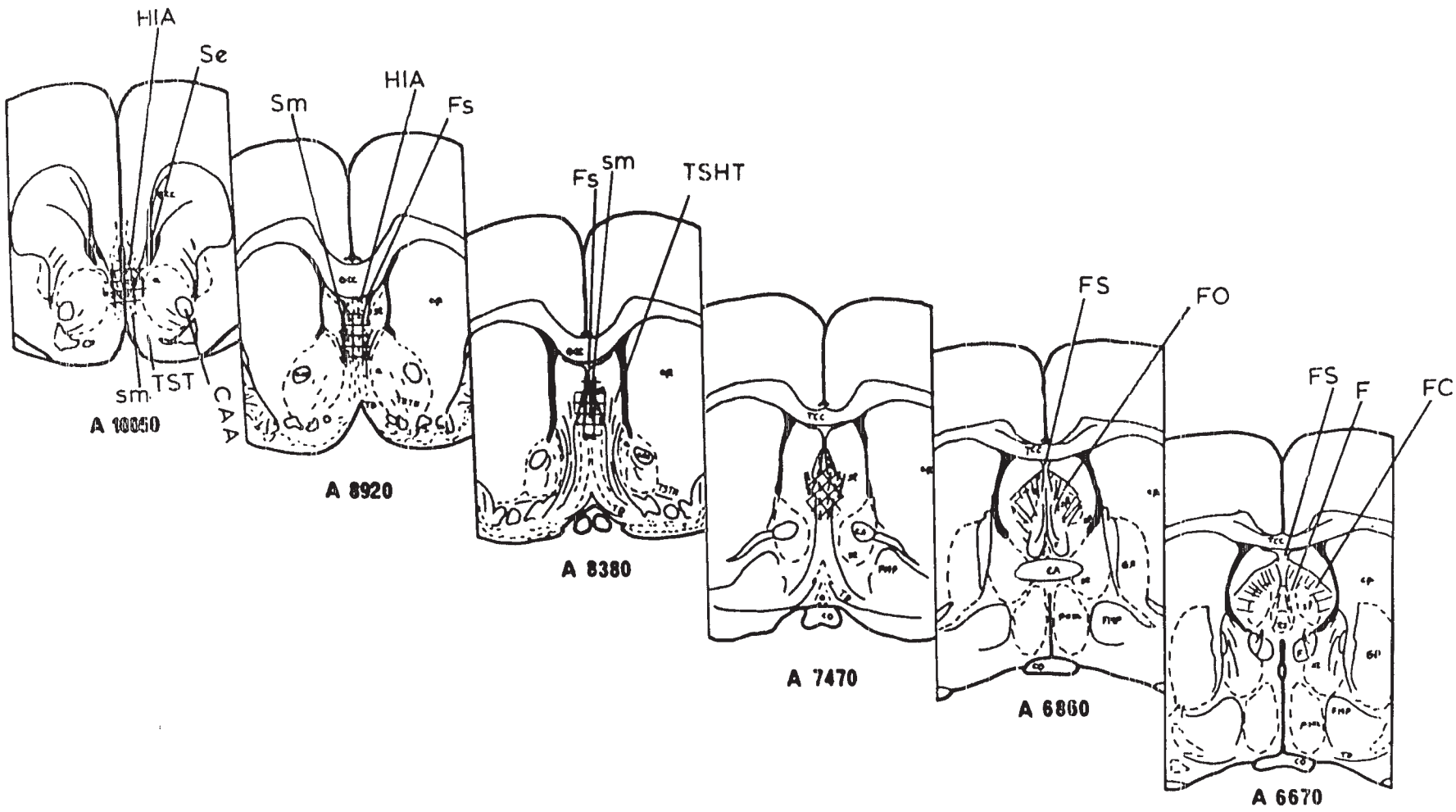

HIA
Se
sm
TST
CAA
A 10650
Sm
HIA
Fs
A 8920
Fs
sm
TSHT
A 8380
A 7470
FS
FO
A 6860
FS
F
FC
A 6670

Fig. 19. Photomicrograph of a coronal section through the septum of S115, showing the extent of damage produced by the lesions.

In only 1 case did an absolute increase in water intake occur without extensive destruction to the ventromedial septum. S121 suffered damage primarily in the anterior lateral septum, including the lateral septal nuclei, the superior fornix and the septo-hypothalamic tract. The anterior dorsal portion of the medial septum may have been slightly damaged.

S118 suffered extensive destruction and degeneration of the area below the anterior commissure, including the medial preoptic area. Since this region is involved in the elaboration of ADH, the destruction of this area may account for the increase in water intake observed in this S. Although degeneration of some cells in this region may have occurred in other Ss, this was not evident when this area was viewed with the microscope under high magnification.

Some structures outside the primary septal area were damaged in a few instances, especially when the electrode had been directed towards the far lateral septum, and involved tissue surrounding the ventricles. Such damage did not appear essential for producing increased water intake. Ss 110 and 115 sustained damage only to septal structures, and these Ss were among those exhibiting the greatest increase in intake. On the other hand, S117 suffered damage to the corpus callosum and caudate-putamen, and this rat showed no change in water consumption.

The results obtained with the guinea pigs are presented in Table 16. In general, these results were similar to those obtained with the septal rats. Only 7 of the 15 Ss which sustained damage to the septum showed an increase in water intake. Two of the remaining 8 Ss (Ss12, 20) became relatively hyperdipsic, while the other 6 Ss showed no change in intake, even when corrected for changes in body weights. As in the rat, hypodipsia was observed during the immediate (24 hr.) post-operative period. Increased water intake, if it occurred, began only on the second or third post-operative day.

Weight loss was observed to be most dramatic in those Ss which increased water intake (Fig. 20). The 2 Ss which became relatively hyperdipsic lost weight of course, but not nearly as much as did the septal drinkers. Neither the remaining experimental animals nor the controls lost any significant amount of weight after surgery. Some of the experimental animals became aphagic for 2 to 3 days after surgery, and S8 never ate during its entire survival period of 6 days following the operation.

For Ss which did show an increase in water intake, the medial septum was usually destroyed or damaged. Drawings of the lesion in each S are presented in Appendix C. A photomicrograph of the lesion in S23, which showed the most dramatic increase, is shown in Fig. 21.

TABLE 16

Pre- and Post-Operative Water Intake Levels of Guinea Pigs with Septal Lesions

S	Water Intake (ml.) Pre-Operative	Post-Operative
1	105.1 ± 3.3	147.3 ± 5.2
2	122.6 ± 2.8	163.8 ± 7.1
4	98.6 ± 2.9	137.4 ± 4.9
5	114.5 ± 3.0	106.6 ± 4.2
7	130.3 ± 2.6	122.8 ± 3.7
8*	107.9 ± 1.8	
10	88.6 ± 1.3	91.4 ± 2.0
12	110.6 ± 2.2	118.8 ± 3.4
13	92.8 ± 3.1	94.6 ± 2.7
14	121.4 ± 2.5	119.6 ± 2.2
17	116.0 ± 3.4	156.7 ± 4.0
18	97.3 ± 2.1	128.6 ± 3.7
19	98.0 ± 1.7	137.8 ± 2.9
20	101.1 ± 2.4	114.3 ± 3.6
23	119.1 ± 3.3	185.6 ± 5.0

* Adipsia and aphagia resulted in death 6 days after surgery.

Values are means ± standard deviations.

Fig. 20. Pre- and post-operative body weights of control (Con) and septal drinker (SD) guinea pigs.

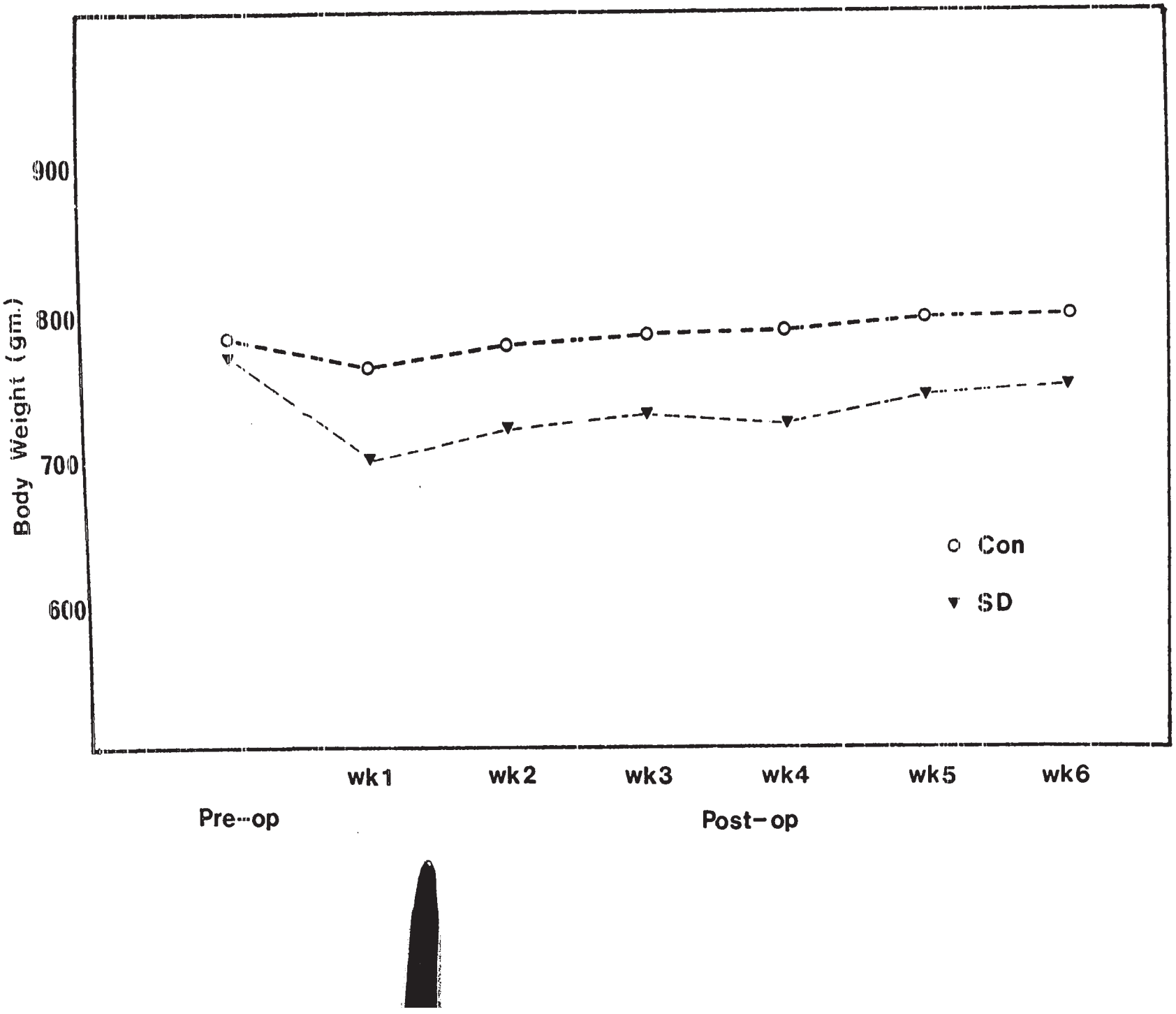

900
800
700
600
Body Weight (gm.)
wk1
wk2
wk3
wk4
wk5
wk6
Pre-op
Post-op
Con
SD

Fig. 21. Photomicrograph of a coronal section through the septum of S23 (guinea pig) showing extent of damage produced by the lesion.

DISCUSSION

The results of this experiment indicate that destruction of a fairly well circumscribed area in the medial septal region of both the rat and guinea pig brain results in increased post-operative water intake. In the present experiment, the type of lesion which increased water intake was smaller than that described by other investigators (Harvey and Hunt, 1965; Donovick and Burright, 1967; Carey, 1967), and those produced in experiments 1 to 5 of the present investigation. However, the general area of the medial septum, shown by this experiment to be an important focus for increased water intake, was included in the larger lesions produced in all of those studies. Thus, the anatomical results of the present experiment are consistent with the data of those investigations.

These results do not necessarily support the conclusion of Lubar et al. (1968) that the posterior one-third of the septum is the critical region for septal hyperdipsia. A recent study by Carey (1969) may clarify this point. Carey made lesions in both the anterior and posterior septum, and found increased water intake following damage to both areas. Important differences did appear however, when the Ss of the 2 groups were tested in operant situations. The Ss with posterior septal lesions were inferior to controls on thirst motivation tasks, whereas anterior septal

lesions slightly enhanced performance in the same tasks. Since many of the septal efferents originate in the region of the medial septal nucleus and pass back through the posterior septum to enter the fornix, it may be that in the latter studies, the outflow from the medial septum was interrupted, resulting in a behavioural change similar to that produced by removing the source of the outflow.

Although destruction of the medial septal region was found to produce absolute hyperdipsia, damage to the lateral regions of the septum usually resulted in relative hyperdipsia. Destruction of both medial and lateral septal tissue usually increased the magnitude of the hyperdipsia. Thus the degree of absolute and relative hyperdipsia which occurs following a septal lesion may depend upon the amount of damage to the medial and lateral septum respectively. Since a reduction in the hyperdipsia may occur several days or weeks after operation, some recovery of function seems possible. This may also depend upon the amount of neural tissue destroyed.

Besch and Van Dyne (1969) suggested that septal hyperdipsia occurs as the result of degeneration in the paraventricular nuclei which leads to reduced secretion of ADH. This interpretation is not supported by the results of the present experiment. With the exception of one animal, no gross degeneration was observed in any of the anter-

ior hypothalamic nuclei, including the medial and lateral preoptic nuclei, the preoptic and hypothalamic paraventricular nuclei or the supraoptic nuclei. Thus, as suggested in an earlier chapter, septal hyperdipsia does not appear to be due to an interference with the ADH system.

All of the animals in the present experiment (both rats and guinea pigs), as well as those in the earlier experiments, which received septal lesions lost weight after surgery. In addition, those animals which became hyperdipsic lost more weight than those which did not increase water intake. Thus a high correlation between weight loss and increased water intake may be obtained following septal damage. Normally, lighter animals tend to drink less water (Cizek, 1965), and the results of the present experiment suggest that septal lesions interfere with the fine balance between water intake and body weight. This may be due to an electrolyte imbalance resulting from the lesion, although there is, as yet, no evidence of this.

The present experiment is the first demonstration that increased water intake results from lesions in the septum of the guinea pig. Although more work needs to be done with other species, these results extend the generality of the observations of septal hyperdipsia in rats, and further emphasize the importance of the septal nuclei in the regulation of water intake.

CHAPTER 8

The results of this study suggest that the septum is involved in an inhibitory or satiety system for the control of water intake. It was observed that septal animals drink no more frequently than controls, nor is the cyclic-diurnal pattern of feeding and drinking disrupted by lesions of the septum. Rather, the bouts of drinking are extremely prolonged after the lesion. Following water deprivation, septal rats drink for much longer periods of time than do normal controls. Similar results were obtained by Donovick and Burright (1968) following two days of water deprivation. Blass and Hanson (1970) have also found that septal rats do not drink more often than controls, but do drink for longer periods once drinking has been initiated. These observations suggest that destruction of the septal nuclei disrupt the animal's ability to utilize or to respond to satiety signals.

The results of the electrical stimulation experiment support the hypothesis that the septum is part of an

inhibitory system, since water intake was reduced by such stimulation in both the ad libitum and water-deprived rat. There are other data which also support this suggestion. Mogenson, McLaughlin, Stevenson and Wishart (1969) found that administration of sodium phenobarbital, which increases water intake in normal rats, has little or no effect in rats with lesions of the septum. They speculated that sodium phenobarbital increases water intake by depressing a satiety system which involves the septal area. Thus, with the septum removed, the drug did not increase water intake. In Chapter 6 of the present study, it was shown that food deprivation also affects water intake in rats with septal lesions. It was suggested that perhaps the mechanisms controlling food and water intakes have common inputs, and that removing the inhibitory influence of the ventro-medial hypothalamus enhances the hyperdipsia resulting from the septal lesion. Finally, as indicated earlier, additional evidence suggesting that the septum has inhibitory effects on the lateral hypothalamus has come from self-stimulation experiments. Lorens (1966) showed that lesions of the septum enhance the rate of responding for electrical stimulation of the lateral hypothalamus. Keesey and Powley (1968) demonstrated that septal lesions reduce the threshold current required for lateral hypothalamic self-stimulation.

What is the mechanism underlying septal hyper-

dipsia? Damage to the septum does not seem to affect the rat's response to osmotic (Lubar et al., 1969; Blass and Hanson, 1970), thermal (Tegart, unpublished observations), or prandial cues (Blass and Hanson, 1970; Chapter 6). Blass and Hanson (1970) have reported that following a hypovolemic stimulus, rats with septal lesions drink more than controls. They have suggested that the septum mediates the inhibition normally exerted on hypovolemic drinking. While little is known about hypovolemic-induced thirst and drinking, Stricker (1969) has shown that one stimulus sufficient to inhibit the drinking induced by hypovolemia is expansion of the intracellular space. He has proposed the existence of a satiety mechanism based on osmotic dilution, in which drinking induced by intravascular dehydration gradually lowers body fluid osmolality below normal. When this occurs a thirst satiety system is excited which inhibits further drinking.

While it is tempting to propose that the septum is part of this inhibitory or satiety system, the evidence that septal rats overrespond to hypovolemia is not conclusive. The results of a recent study fail to show that rats with septal lesions differ from controls in their response to hypovolemia (Tegart, unpublished observations). Clearly, there is a need for additional research directed at elucidating the inputs to the septum, and to the inte-

gration which occurs there. In particular, the observations of Blass and Hanson (1970), indicating that septal lesions lead to a loss of the inhibition exerted on hypovolemic drinking, need to be replicated, since the type of deficit they propose could account for the observations of the present study which indicate that the septum is involved in a satiety system.

As indicated in the introduction, the hypothalamus appears to be an important component of the integrative-control system for water intake. The lateral hypothalamus in particular is involved in this system since drinking can be initiated by electrical or chemical stimulation of this area (Mogenson and Stevenson, 1966, 1967; Grossman, 1960, 1962), whereas lesions of the lateral hypothalamus lead to adipsia (Montemurro and Stevenson, 1957). A model for the control of water intake has been provided by Oatley (1967), in which the integrative-control system for water intake is affected by various peripheral and central influences. Thus, the inhibitory influences of the septum are probably exerted on the hypothalamic drinking system.

There is ample evidence of reciprocal connections between the septum and hippocampus. The caudal projections of the septum into the medial forebrain bundle are, for the most part, complementary to the ascending systems from the hypothalamus and midbrain. Small lesions placed in

either the medial or lateral septum result in degeneration in the medial forebrain bundle, with the degenerating fibers becoming fewer and fewer as the fiber pathway courses through the hypothalamus to the midbrain (Raisman, 1966). Thus the septum gives rise to fibers which terminate in many of the hypothalamic nuclei. Although most of these fibers sysnapse either in the preoptic area or in the lateral hypothalamus, strong septal connections are extablished with the dorsomedial, the posterior, and the dorsal premammillary nuclei. In addition, Sutin (1963) using the evoked potential technique, has proposed the existence of direct, monosynaptic fibers from the septum to the ventromedial nucleus.

Since a large proportion of the septal efferents terminate in the anterior hypothalamus-preoptic area, the inhibitory influences of the septum may be mediated through this region. Smith and McCann (1962) have proposed that this region exerts an inhibitory influence over the lateral hypothalamic drinking system. Together with the septum, this area may be involved in an inhibitory system concerned with the termination of drinking. On the other hand, there are direct pathways from the septum to the lateral hypothalamus, and the inhibition from the septum may be monosynaptic. Miller and Mogenson (1969) have provided preliminary evidence that the septal region influences the activity of

cells in the lateral hypothalamus. Electrical stimulation of the anterior septum was found to suppress the discharge rate of neurons in the lateral hypothalamus, whereas stimulation of the posterior septum resulted in both enhancement and suppression of the discharges of the same cells. Clearly, additional research is required before any positive conclusions can be drawn concerning the functional connections mediating septal hyperdipsia.

Although the results of the present study suggest that the septum is involved in an inhibitory system for the control of water intake, the chemical stimulation experiments indicate that the septum also provides facilitative influences to the system controlling water intake (Fisher and Coury, 1962; Grossman, 1964; Coury, 1967). However, the inhibitory influences of the septal region seem to be the more potent, since hyperdipsia rather than hypodipsia occurs as a result of septal damage. The facilitatory system may be involved in the taste aspects of consummatory behaviour, since animals which received carbachol in the septal region were found to prefer a sucrose solution to water (Gandelman et al., 1968). This suggestion is supported by the observations of Beatty and Schwartzbaum (1968) that septal animals are more 'finicky' in their acceptance and rejection of sweet and bitter solutions than are normal controls.

Although much of the empirical data suggests that septal hyperdipsia is not due to a disruption of the ADH system leading to an inability to concentrate urine, there is no conclusive evidence that the increased water intake is not secondary to some other effect of the lesion. More work needs to be done on the effects of septal lesions on the various physiological mechanisms controlling urine output. In particular, studies of adrenal gland and kidney functions and electrolyte metabolism are required, since both urine output and water intake are, in part, controlled by these factors.

Although the possibility of a central satiety system has been recognized for many years, there has been a general lack of empirical data proving the existence of such a system. Oatley (1967) has suggested a short-term store which receives information from receptors, and which inhibits the system controlling water intake. The results of the present series of experiments provide preliminary evidence of a central inhibitory or satiety mechanism, involving the septal region. Some speculation about the advantages of a short-term satiety system for water intake seems warranted. Water intoxication is potentially lethal, but even if death does not occur, overhydration has unpleasant side effects including vomiting and coma. In the absence of a metering system, drinking once initiated,

would continue unabated until the original water deficit conditions were reversed. Since time is required for the absorption of water through the gut-wall into the body fluids, excess water would be ingested each time the animal drank, resulting in overhydration. As Deutsch (1960) has emphasized, it appears that while a water deficit serves to activate receptors which signal water lack and to initiate thirst and drinking, it is the act of drinking that temporarily serves to inhibit further drinking. It appears that the septum is part of a neural mechanism responsible for the inhibition exerted upon the drinking system soon after water intake begins.

CHAPTER 9

SUMMARY

An investigation was conducted into the nature of the hyperdipsia resulting from septal lesions. In Chapter 2, the basic phenomenon of septal hyperdipsia was examined, and it was found that polyuria always preceded hyperdipsia, which developed only several days after surgery. Rats with septal lesions usually lost weight during the first week after surgery, but thereafter gained weight at the same rate as controls. Increased water intake was observed up to four months after the lesion was placed, indicating the permanence of septal hyperdipsia. There was no consistent relationship between hyperemotionality and hyperdipsia from septal lesions, indicating that these two behaviours are mediated by different mechanisms.

In the second experiment, the pattern of feeding and drinking in rats with septal lesions was examined. It was found that septal lesions do not disrupt the cyclic-diurnal feeding and drinking pattern of rats, nor is the frequency of drinking increased by the lesion. Rather, once drinking has been initiated, following either feeding or water deprivation, the septal rat engages in longer bouts of drinking than controls. Damage to the septum appears to

disturb a mechanism concerned with the termination or cessation of drinking.

The results of the third experiment, together with data from previous experiments, suggest that increased thirst is not the only or entire cause of septal hyperdipsia. Septal rats, which were hyperdipsic in the home cage when water was freely available or when required to make an operant response for each water reward, would not work at high work-rates to obtain excess water. Water or food deprivation enhanced the operant responding behaviour of the rats with septal lesions, and it was suggested that this reflected a dysfunction in incentive-reward processes following the lesion.

Some support was obtained for the hypothesis that the system regulating water intake receives inhibitory influences from the septum. In the fourth experiment, intermittent septal stimulation reduced water intake in both the sated and water deprived rat. In the fifth experiment, food deprivation affected water intake in the rats with septal lesions in a different way than it did in normal controls. Septal rats remained or became hyperdipsic during a period of food restriction, while normal rats reduced their water intake. It was suggested that the systems controlling water and food intakes have common inputs, and that removing the inhibitory effects of the ventro-medial hypothalamus further enhances the hyperdipsia.

Finally, in the last experiment, some evidence was obtained which indicated that damage to the medial septum alone is sufficient to produce hyperdipsia. In addition, destruction of the septum in the guinea pig was found to result in increased water intake, extending the generality of the results obtained in the rat.

The results of this study indicate that lesions of the septum disrupt the animal's ability to utilize short-term satiety cues. It was suggested that the septum is involved in a mechanism concerned with the termination of water intake, and that it exerts an inhibitory influence either directly, or indirectly through the preoptic area, upon the lateral hypothalamus, resulting in the cessation of drinking.

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APPENDIX A

TABLE 1

Summary of Analysis of Variance

Source	SS	df	MS	F
Between Ss	4842.9	23		
A (lesion)	4559.6	1	4559.6	354.1*
Error	283.3	22	12.9	
Within Ss	58837.7	96		
B (schedule)	56195.2	4	14048.8	1076.8*
AB	1494.4	4	373.6	28.6*
B X Ss	1148.1	88	13.0	
Total	63680.7	119		

* Significant at .001 level.

TABLE 2

Summary of Analysis of Variance

Source	SS	df	MS	F
Between Ss	3971.6	23		
A (lesion)	952.0	1	952.0	6.9*
Error	3019.6	22	137.2	
Within Ss	17173.9	96		
B (schedule)	14079.5	4	3519.9	246.1*
AB	1838.3	4	459.5	32.1*
Error	1256.1	88	14.3	
Total	21145.5	119		

* Significant at .001 level.

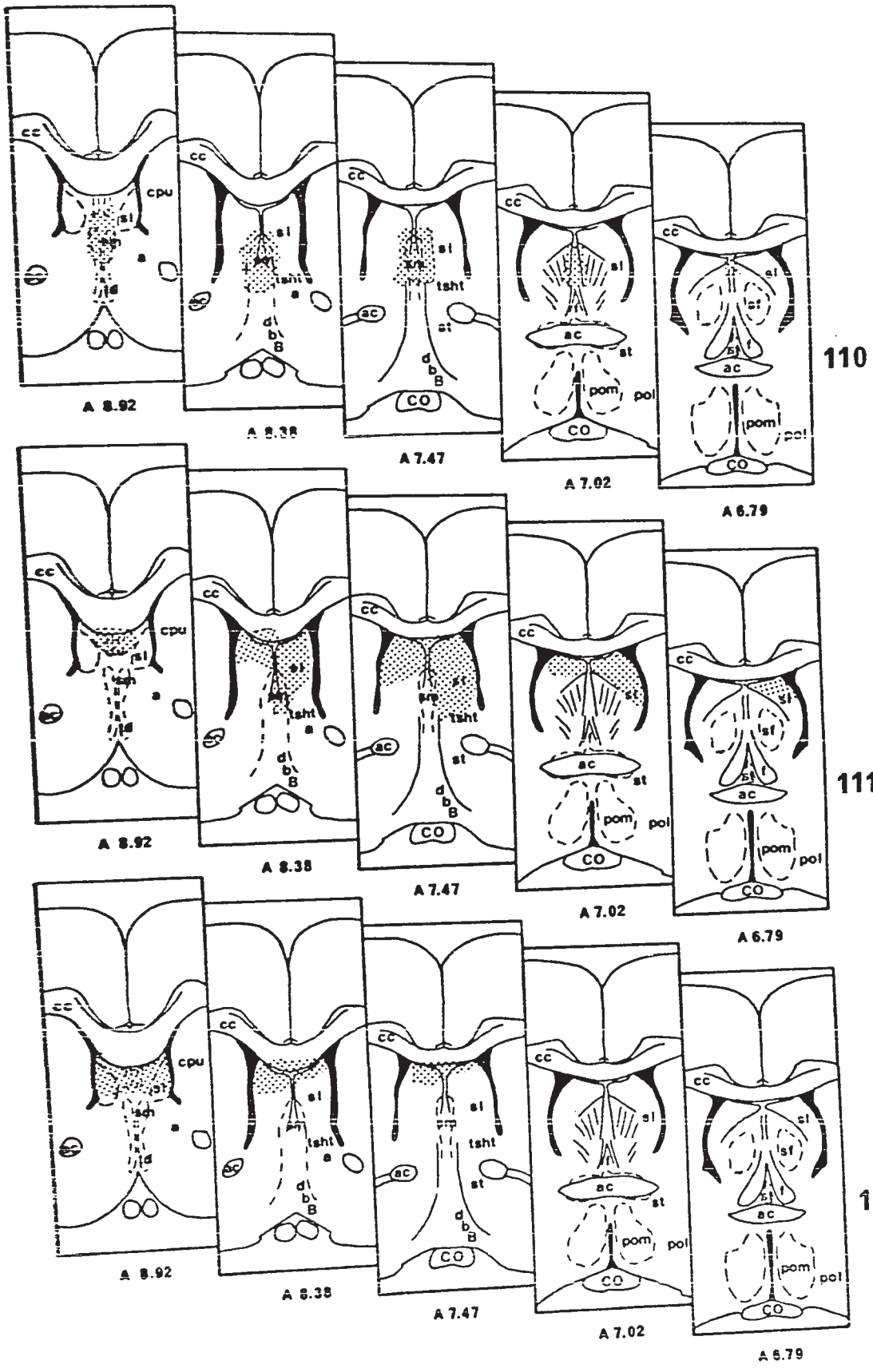
TABLE 3

Summary of Analysis of Variance

Source	SS	df	MS	F
Between Ss	510.4	23		
A (lesion)	423.8	1	423.8	107.4*
Error	86.7	22	3.9	
Within Ss	873.4	168		
B (schedule)	318.5	7	45.5	48.1*
AB	408.7	7	58.3	61.7*
Error	145.8	154	.9	
Total	1383.5	191		

* Significant at .001 level.

APPENDIX B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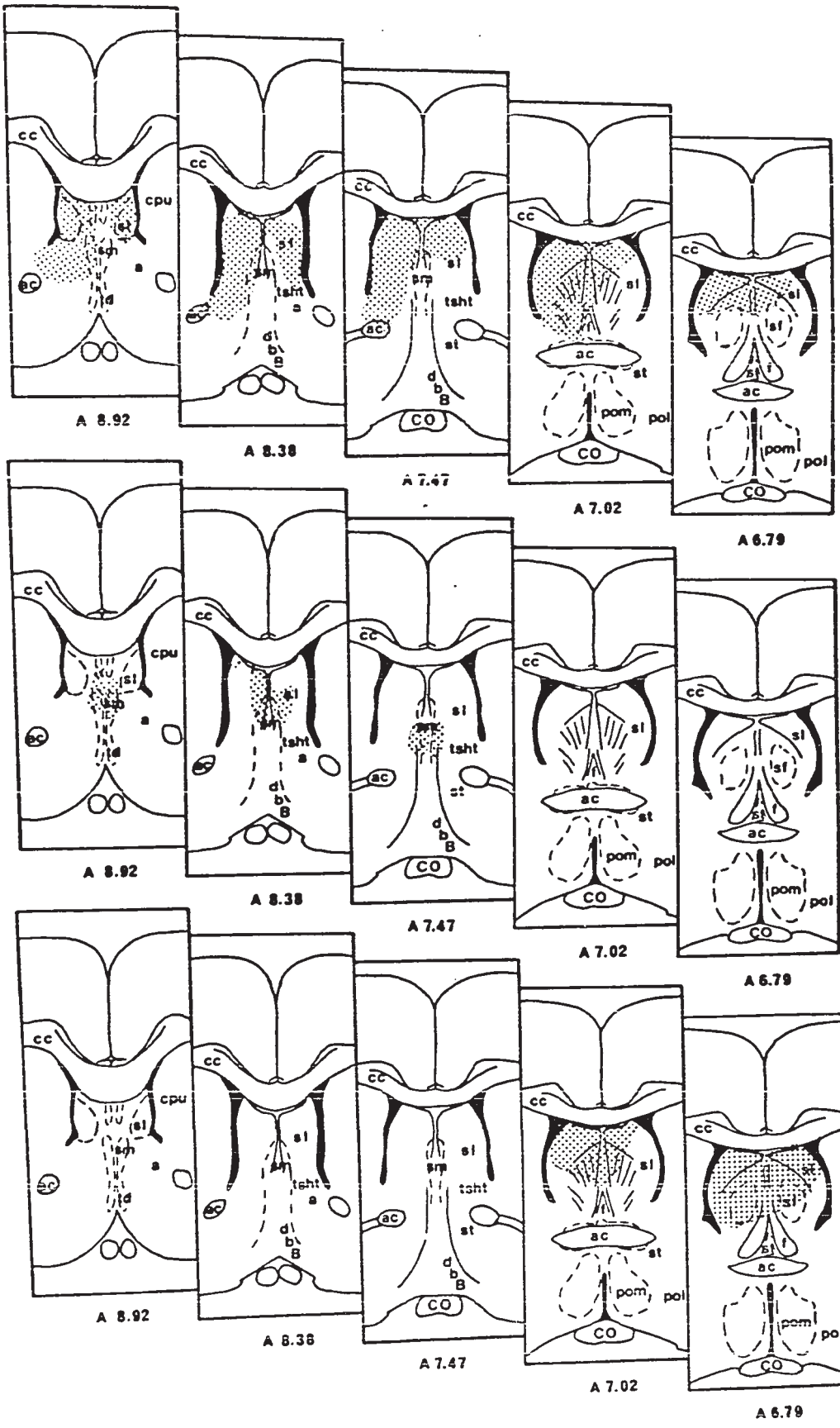
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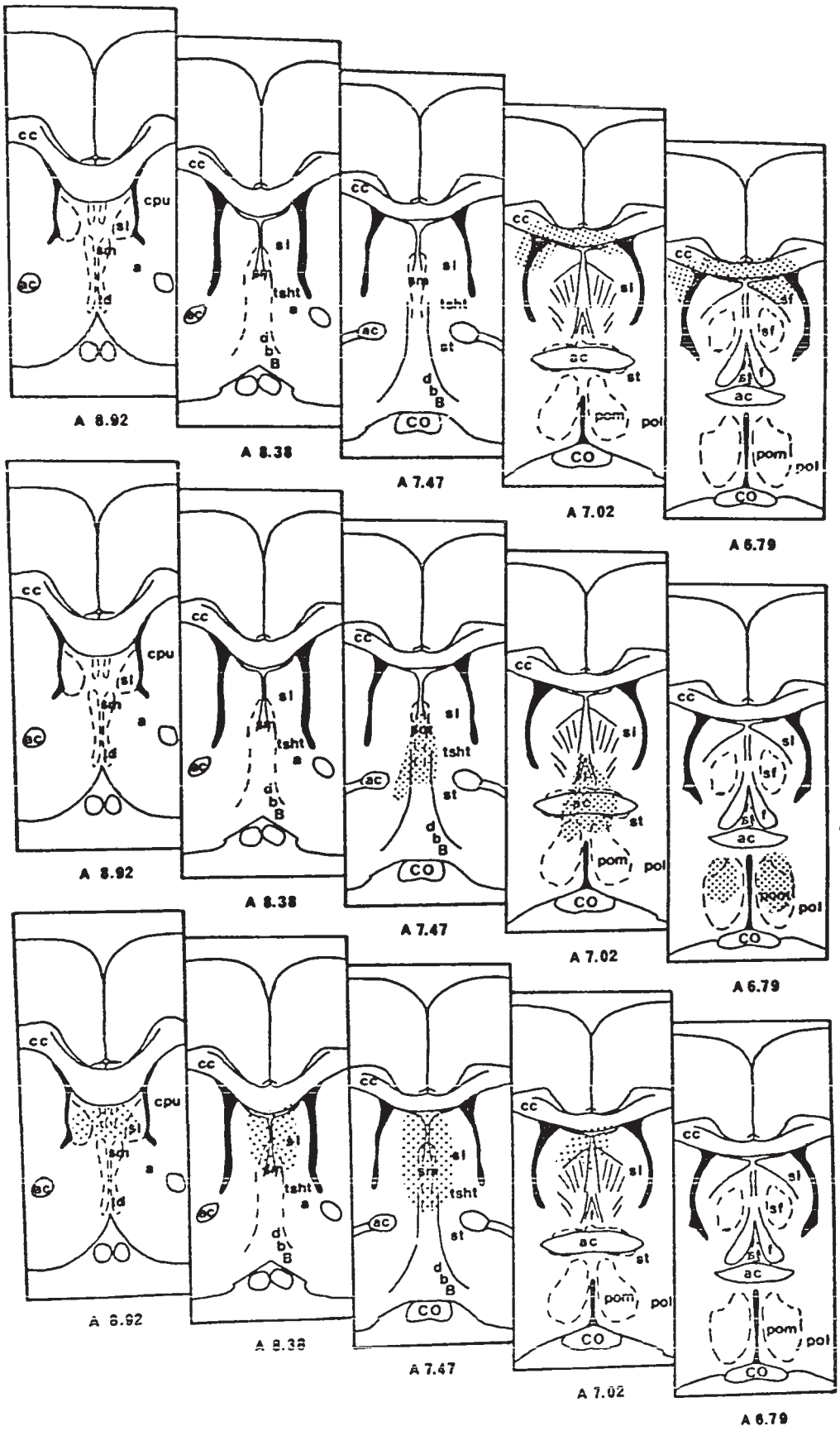
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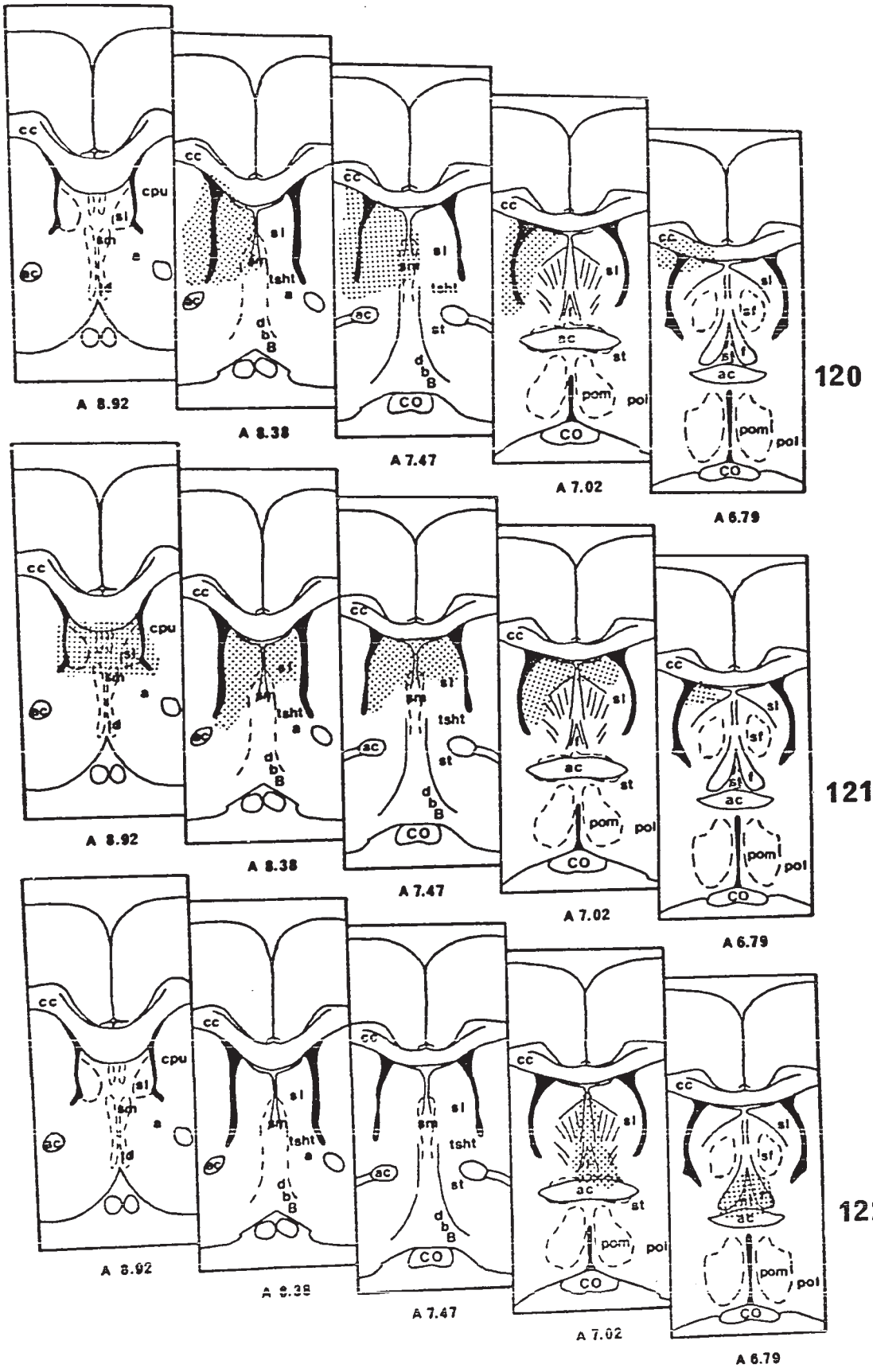
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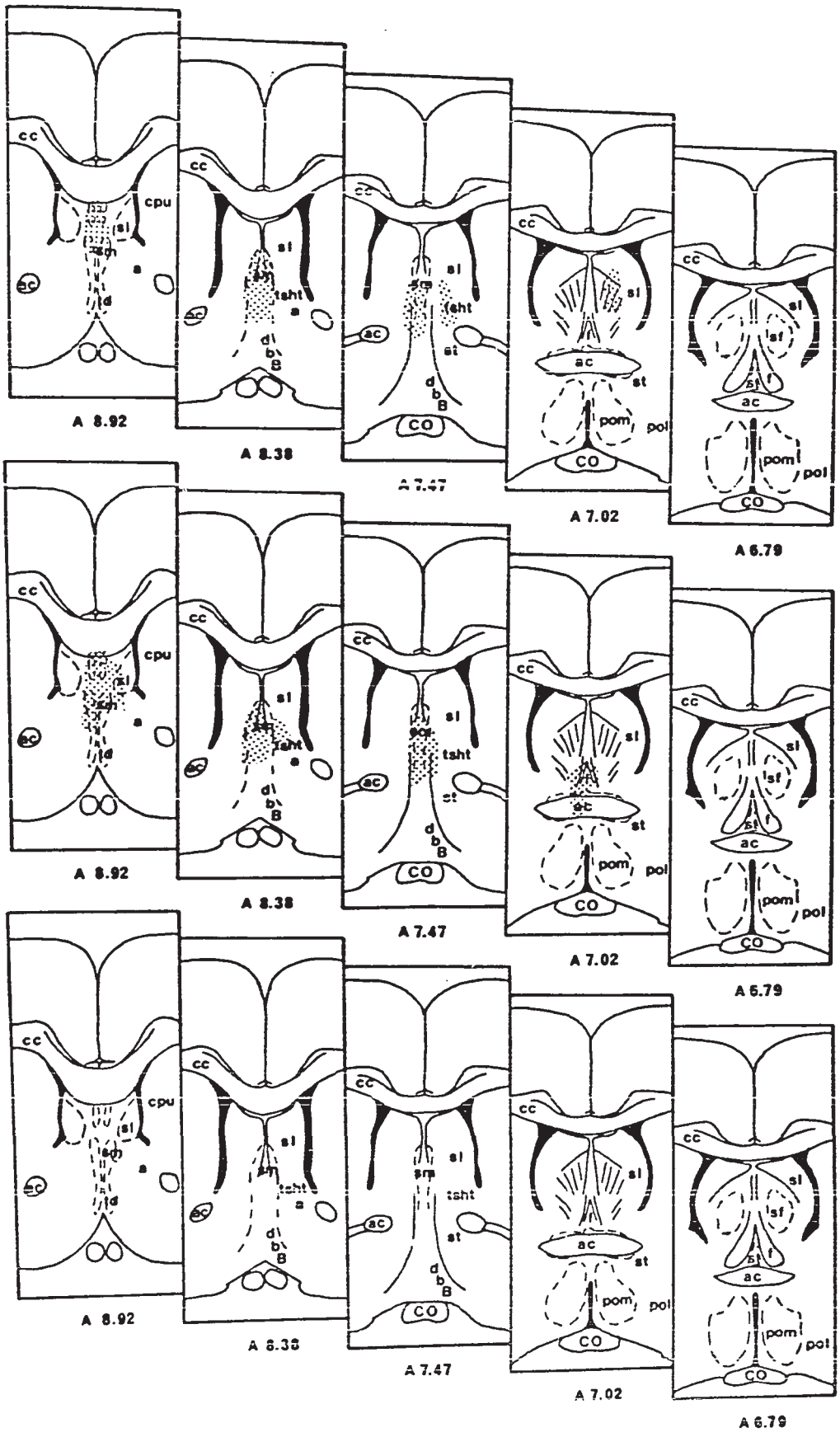
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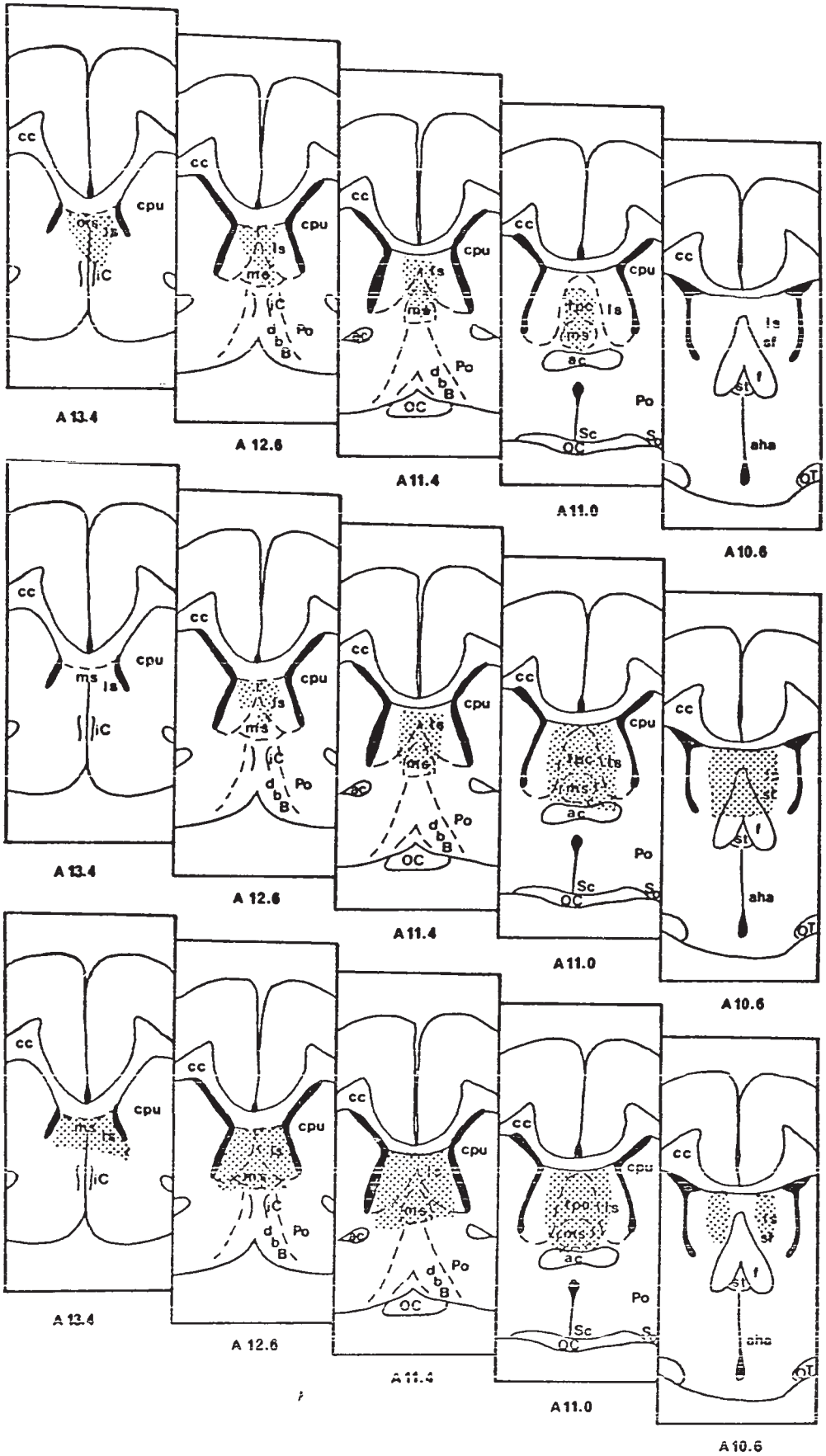
APPENDIX C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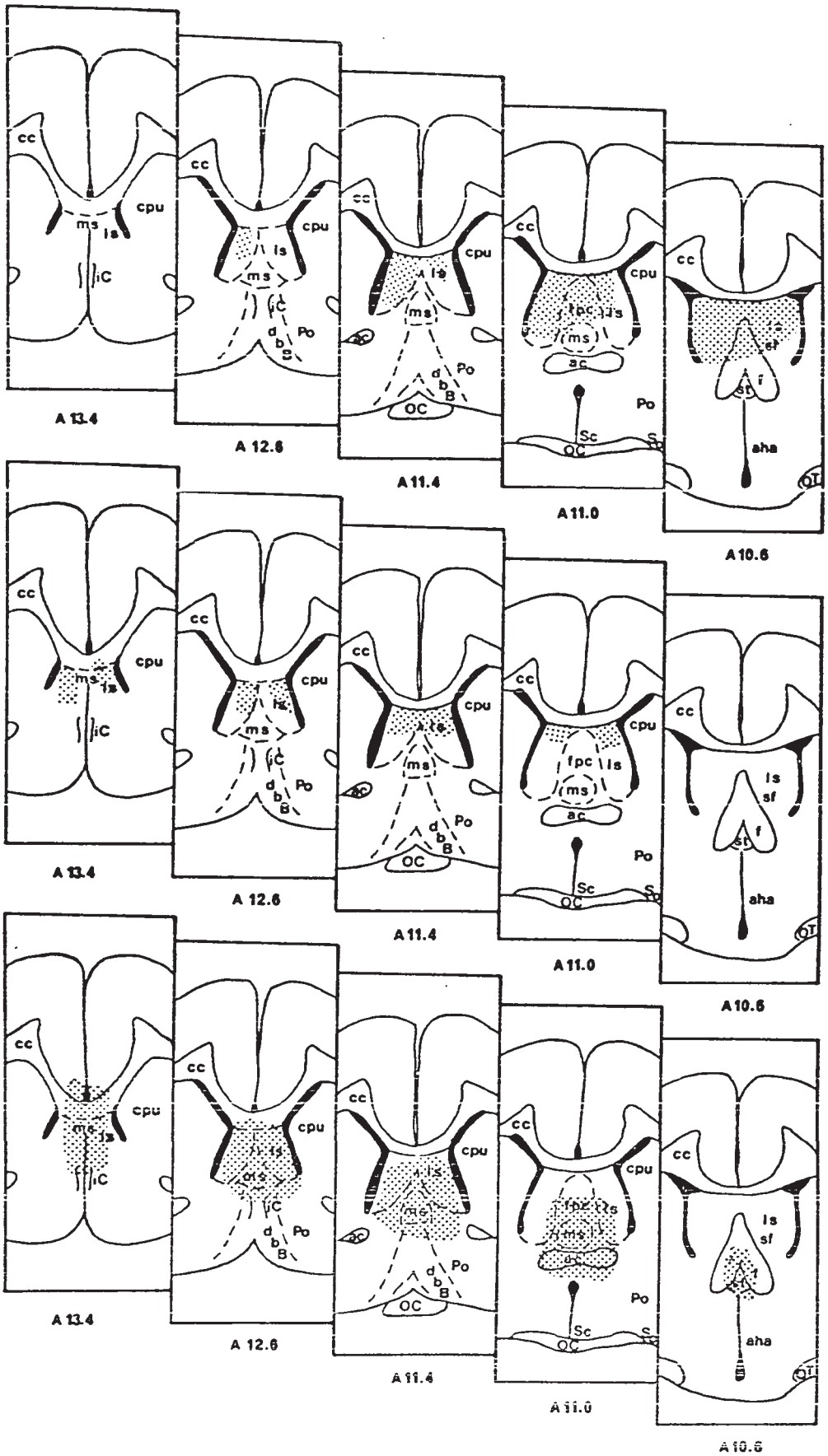
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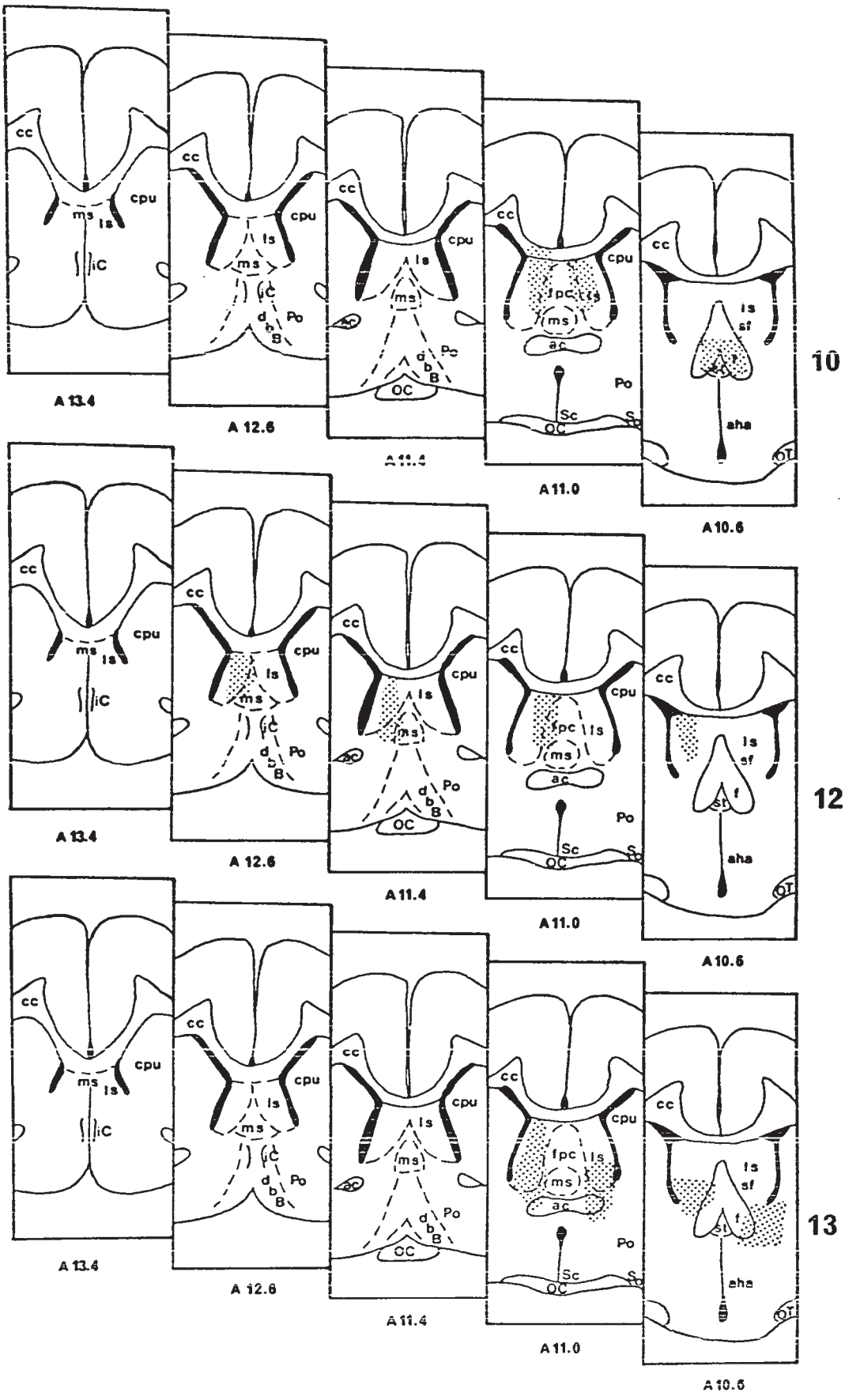
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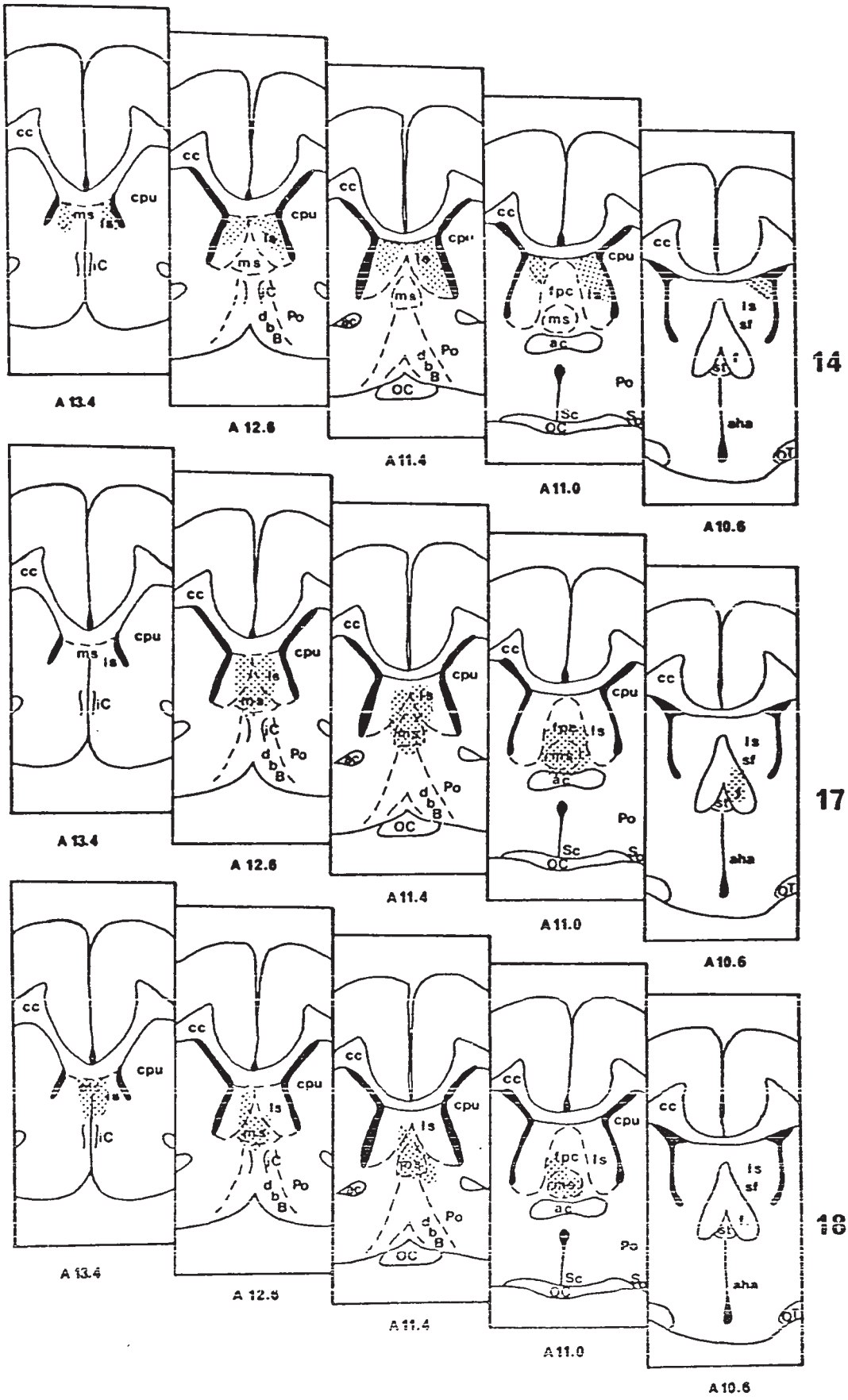
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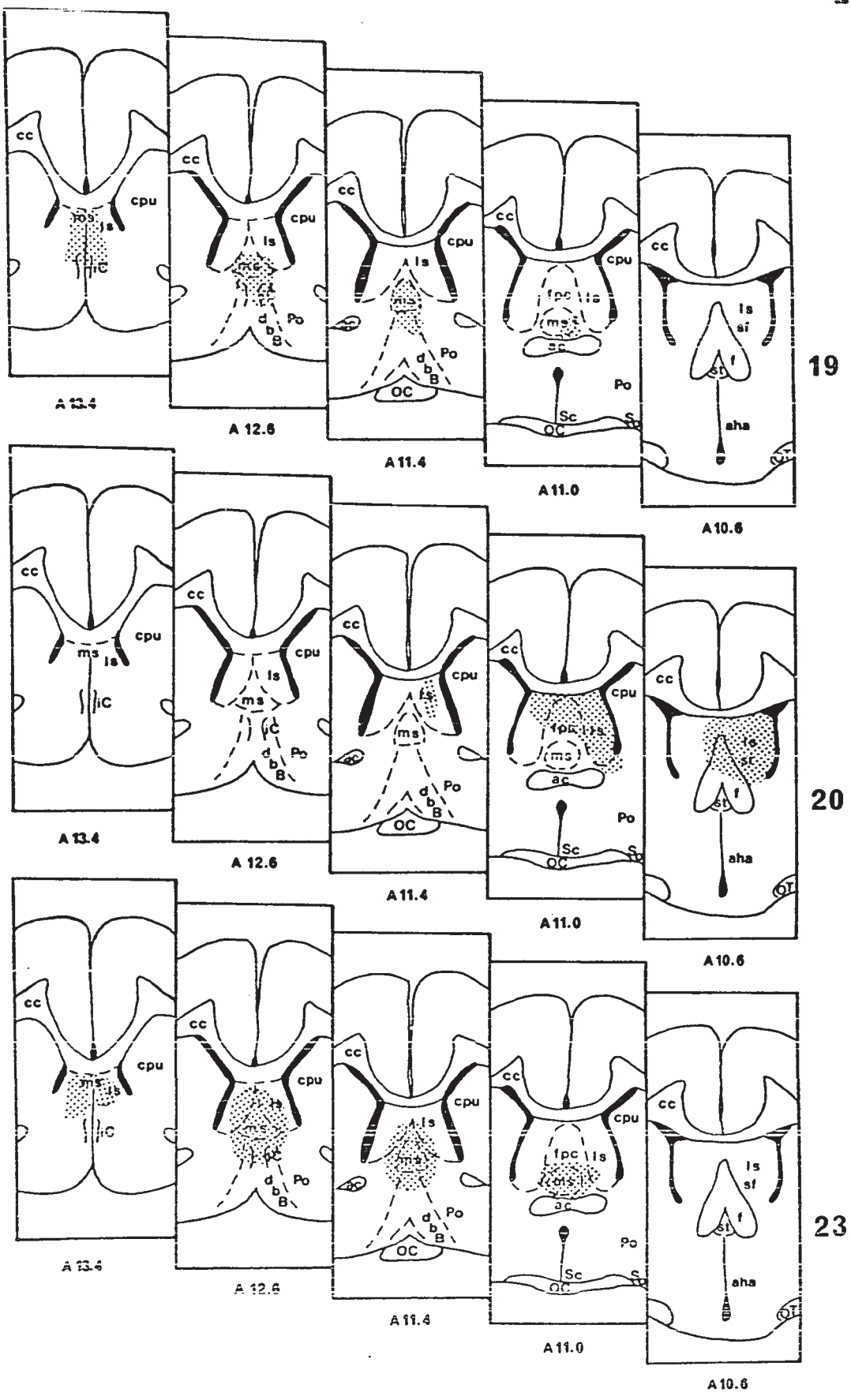
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